ANTIBIOTIC POLICY IN DUTCH HOSPITALS

A survey of Dutch antibiotic formularies

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A survey of Dutch antibiotic formularies

een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

Proefschrift

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door

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te Koog aan de Zaan

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CHAPTER I

INTRODUCTION

R. Janknegt

Multiple antibiotic resistance has become a major problem in many European countries and the United States. The importance of a rational antibiotic policy is stressed both nationally and internationally to prevent the possible development of resistance due to unjustified use of antimicrobial agents (1).
Financial aspects also play a role in antibiotic policy. The total cost of the in-hospital use of antimicrobial agents has increased by 30% from 1978 to 1986 (2).
One of the aims of the "WHO Program for appropriate healthcare technology" is to reach a justified use of technologies (antibiotics) (3). Also the Dutch "Health Council" (Gezondheidsraad) has underlined the importance of a rational antibiotic policy, based on regular surveillance of (local) bacterial resistance patterns (4).
Most Dutch hospitals have created so-called "antibiotic formularies" with guidelines for the treatment of infectious diseases which are specific for that hospital or for a group of collaborating hospitals (regional antibiotic formularies).
In 1988 - 1989 the Dutch Medical Audit organisation CBO (Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing) investigated the availability of antibiotic formularies in Dutch hospitals (5). The authors concluded that most hospitals followed the recommendations of the Gezondheidsraad and they expected that the situation would improve with an increasing degree of automation in bacteriological laboratories.
The antibiotic policy in Dutch hospitals is the subject of this thesis.
An overview of the general contents of these antibiotic formularies in Dutch hospitals (in 1991) is presented in this chapter.
The relationship between antibiotic policy guidelines and the actual use of antimicrobial agents has not been studied extensively. We have correlated the antibiotic guidelines from 20 Dutch hospitals with the actual use of several groups of antimicrobial agents, such as aminoglycosides, co-trimoxazole, second and third generation cephalosporins, co-amoxiclav (amoxycillin + clavulanic acid), macrolides, antipseudomonal penicillins and fluoroquinolones. This study is presented in Chapter 2.
Most Belgian hospitals do not have a written antibiotic policy, but they use a formulary, which is adapted to the Belgian situation

from the antibiotic formulary written by Dr. J.P. Sanford from Bethesda, Maryland, USA. It is not clear whether the use of one formulary in the whole country offers advantages in a more uniform use of antimicrobial agents. In Germany most hospitals do not have written guidelines for the treatment of infections. Because the data on the actual use of antimicrobial agents in hospitals in several European countries are very limited, we compared the use of antibacterial drugs in Dutch hospitals to the use of these drugs in hospitals in Germany (Nordrhein Westfalen) and Belgium (both from the Dutch speaking and French speaking parts), expressed as the number of Defined Daily Doses (DDD) per 100 bed days and tried to correlate the differences in antibiotic use with differences in antibiotic policy in these countries. This study is described in Chapter 3.

The recommendations of the Dutch antibiotic formularies for the treatment of several categories of infections are given in Chapters 4-6. Chapter 4 presents the guidelines for the treatment of bacterial bronchitis, with special reference to the definitions of bronchitis used by these formularies. Chapter 5 contains the guidelines for the treatment of pneumonia. The antibiotic policy for the treatment of sepsis is summarized in Chapter 6.

The recommendations of the formularies for three different types of bowel surgery (colorectal surgery, biliary surgery and gastroduodenal surgery) are reported in Chapter 7 and those for the prophylactic use of antibacterial drugs in gynaecological surgery (abdominal hysterectomy, vaginal hysterectomy and caesarian section) are presented in Chapter 8.

Aminoglycosides are important antimicrobial drugs, but their use is limited by the relatively high incidence of nephrotoxicity and ototoxicity. Monitoring of these drugs is therefore considered necessary. Animal studies have indicated that once daily dosage of aminoglycosides is associated with a lower incidence of toxicity and this has been confirmed in several human studies. The guidelines for drug monitoring of aminoglycosides in clinical practice are still based on the conventional 3 times daily dosing schedule. The current guidelines in Dutch hospitals for the dosing schedules for aminoglycosides in relation to the recommendations for drug monitoring were studied by means of an inquiry among

hospital pharmacists. This study is described in Chapter 9.
The choice of a drug from a more or less large pharmaceutical group is often based on criteria which are not always rational and therefore not open for discussion. A rational drug-decision making system has been proposed to make the criteria on which a decision is based transparent, the so-called System of Objective Judgement Analysis (SOJA-system). A number of both national (number of registered indications, number of formulations, cost, etc) and international criteria (efficacy, side-effects, pharmacokinetics, etc) are defined. The SOJA score for the fluoroquinolones ciprofloxacin, ofloxacin and pefloxacin is presented in Chapter 10.
The introduction of oral third generation cephalosporins, such as cefixime and cefpodoxime proxetil on the market has widened the possibilities for sequential therapy with intravenous and oral cephalosporins for infections in hospitalized patients. The theoretical and practical aspects of such therapy are described in Chapter 11.
In Chapter 12 conclusions and recommendations regarding antibiotic policy based on the preceding chapters are given.

MATERIALS AND METHODS

In April/May 1991, 109 members of the Dutch Association of Hospital Pharmacists (NVZA) were given a short description of the aims of the study and they were requested to send to us the most recent version of the antimicrobial formulary used in their hospital.
Data on antibiotic resistance patterns were requested from the microbiological laboratory of all hospitals from which an antibiotic formulary was received.

The following items in the antibiotic formularies were recorded:
- year of publication
- composition of the editorial board of the formulary
- the "weight" of the recommendations in the formulary

- the contents of the antibiotic formularies with regard to
  - general guidelines for the duration of antibiotic therapy
  - antiviral therapy
  - dosage recommendations for children
  - dosage recommendations for patients with renal insufficiency
  - guidelines concerning the use of antimicrobial agents during pregnancy and lactation
  - contra-indications
  - drug interactions, or interactions with food.

Regarding the resistance patterns our prime interest was in the availability of these data. The data were analysed to see whether the antibiotic susceptibility data came from one hospital only or were regional data. Finally, we checked whether it was possible to specify the susceptibility patterns per species, per sample and per ward.

RESULTS

A total of 38 formularies, in use in 78 hospitals, were received from 6 (out of 8) university hospitals (75%) and from 21 out of 40 hospitals with 500 or more beds (53%). Hospitals with fewer than 500 beds but which were part of a conglomerate of hospitals or a region (n = 25) were included in this category. A total of 11 formularies were received from 34 hospitals (32%) with less than 500 beds

No antibiotic formulary was available from 31 hospitals: fourteen of these had no intention of developing their own antibiotic formulary, six hospitals were working on a revision of the antibiotic policy and they considered the present version as "too old" to be submitted to us. A first version of an antibiotic policy would "soon" be available in 9 hospitals, although no specification of the time was given. Two hospitals had only developed guidelines for the prophylactic use of antimicrobial agents.

The year of publication ranged from 1983 to 1991. Fifteen antibiotic formularies were dated before 1988 (Table 1).

TABLE 1

YEAR OF PUBLICATION OF ANTIBIOTIC FORMULARIES

Year	Number of formularies
1983	1
1984	0
1985	2
1986	3
1987	9
1988	5
1989	6
1990	5
1991	7

The editorial board of the antibiotic formularies consisted of a medical microbiologist and a hospital pharmacist in all cases. Other members of the board were internists (66%), surgeons (44%), paediatricians (31%) and chest physicians (19%). All other specialists accounted for only 6%. Twenty-two of the 38 formularies (58%) provided some specifications of the importance of the guidelines. In three formularies it was stated that the guidelines were compulsory and 19 formularies stated that the formulary gave treatment recommendations. In the other 16 formularies (42%) no specification of the importance of the guidelines was given.

The contents of the formularies are given in Table 2.

Guidelines for dose adaptation in patients with renal insufficiency and in children were given in all formularies from university hospitals, whereas these data were present in 40% of the formularies from hospitals with > 500 beds but in 67% of the hospitals with < 500 beds.

Some data on bacterial resistance patterns were available from 22 of the 78 hospitals. The degree of usefulness for the preparation of an antibiotic formulary was highly variable. One hospital recorded the susceptibility of *Pseudomonas aeruginosa* as an indicator organism for the antibiotic-resistance pattern (6). From two other hospitals data were available from blood isolates on the intensive care unit. From 14 hospitals only total susceptibility data for all isolates (without further specification) were available. Eleven of these hospitals were able to discriminate between the source (blood, urine, sputum). For 42 hospitals regional susceptibility patterns were available, whereas 14 hospitals had no accessible information at all on the antibiotic susceptibility data in the hospital. Only 5 hospitals provided data per micro-organism, per material and per hospital ward or outpatient clinic.

TABLE 2

CHARACTERISTICS OF ANTIBIOTIC FORMULARIES
Percentage of formularies in which a certain item is included

Item	Type of hospital University	>500 beds	<500 beds
Duration	60	41	38
Viral infections	80	23	23
Children dosage	100	74	76
Renal impairment	100	40	52
Pregnancy	40	18	30
Contra-indications	40	8	23
Interactions	60	36	23
Trade names	60	63	76
Daily cost	40	5	14

DISCUSSION

In the ideal situation the antibiotic policy should be based on the susceptibility data from the hospital in question with regard to source of the material, such as blood, urine, sputum etc. (7). Data on the local bacterial population are necessary, due to potential differences between hospitals regarding size, the number of intensive care beds, antibiotic policy and the patient population. The presence of certain specialties such as burns centres, oncology and transplantation surgery units will influence the antibiotic policy and also the antibiotic resistance patterns.
These data were available from five hospitals only, however. It is not clear how strong the basis is on which the antibiotic policy of hospitals which have no data on antimicrobial susceptibility is built. This is now often based on a "general impression" from the laboratory results. An antibiotic formulary per hospital is recommended if there are important differences between hospitals in a single region.

A regional antibiotic policy however, has advantages concerning the standardisation of antibiotic utilisation within the region in question. This leads to better cooperation between general practice and hospital use of antibiotics (8). A regional formulary may even be recommendable if the differences in antibiotic susceptibility between hospitals are taken into consideration during the discussion on antibiotic policy.

The results of this inquiry show that the situation regarding the availability of antibiotic formularies in The Netherlands is not ideal. The most important motivation for an optimal use of antimicrobial agents is the relationship between antibiotic use and antibiotic resistance (9). Although various factors are involved in the development of resistance or in the selection of resistant micro-organisms an antibiotic policy is essential for preventing the rapid and wide-spread development of resistance. An optimal antimicrobial therapy, concerning choice of antimicrobial drug, dosage and duration, minimises the development of resistance. The dose should be based on the pharmacokinetic and pharmacodynamic properties of the agent in question, the duration should be determined by clinical studies and by the clinical situation of the patient. The choice of an antimicrobial agent for a specific infection should be based on the susceptibility data from the hospital in question. Both the WHO and the Gezondheidsraad have stressed the necessity of a correct use of antimicrobial agents (3, 4). The situation in 1991 had not greatly improved since 1988 - 1989 (5). In 1991, 31 of the 109 hospitals had no written guidelines for antibiotic policy, whereas 20 of the 38 formularies were at least 3 years old. Taking into consideration the introduction of a number of new antimicrobial agents since 1988, such as the fluoroquinolones, new macrolides and oral third generation cephalosporins, it seems doubtful whether the recommendations in the older formularies are still up-to-date. Only 8% of all formularies clearly state that the formulary is compulsory. The guidelines in the other 92% are not defined as being very strict. It is not clear whether "guidelines" for antibiotic policy will be followed by all clinicians.

I recommend an active policy in the hospitals concerning the preparation of an antimicrobial formulary. This means that a formulary should be revised every 2 years. The choice of antibiotics should be based on susceptibility data from the microbiological laboratory. It is important to define prospectively whether the contents of the formulary are intended as guidelines or whether they are binding. An input from all clinicians is essential in the preparation of the formulary.

The formulary should be evaluated with the medical staff on a regular basis to optimise the antibiotic policy.

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CHAPTER II

ANTIBIOTIC GUIDELINES AND ANTIBIOTIC UTILISATION IN DUTCH HOSPITALS

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SUMMARY

In April-May 1991 the availability of antibiotic formularies in Dutch hospitals was analysed as well as data available on antibiotic susceptibility patterns. In addition data on the use of different groups of antimicrobial agents (aminoglycosides, ß lactam compounds including aztreonam and imipenem, co-trimoxazole, vancomycin and fluoroquinolones) were collected by a questionnaire.
Thirty-eight formularies were received which were used in 78 hospitals. No formulary was available from 31 hospitals: 15 hospitals dit not have the intention to set up antibiotic guidelines, nine hospitals started up with their first formulary and seven used a revised version of the existing one.
Fifteen formularies dated from 1987 or earlier. The availability of antibiotic susceptibility patterns ranged from no data at all (n=14) to extensive data per species, per material and per ward (n=5).
From 20 hospitals data on antibiotic usage as well as on antibiotic guidelines were obtained. Because several hospitals used the same formulary, 15 different formularies were analyzed from 20 hospitals. Fluoroquinolones were used in all hospitals, but were only mentioned in the formularies of 6 hospitals.
The data in the present study underscore the need for a collaborative approach of medical staff, hospital pharmacy and microbiologist in order to maintain a relatively low level of antibiotic resistance in Dutch hospitals.

INTRODUCTION

There is a growing concern over the increased use of antimicrobial agents and the subsequent increase in bacterial resistance and in health care costs (1, 2). Therefore worldwide attempts have been made to optimize the use of antibiotics (3). For instance the WHO participated in meetings and the Infectious Diseases Society of America (IDSA) prepared guidelines to improve the usage of antimicrobial agents (4, 5). The recommendations include the appointment of an antimicrobial agents team given the task of setting up a formulary to encourage the better use of antimicrobial

agents. In addition, the use of these compounds has to be analysed periodically to monitor whether the guidelines of the formulary are still being followed. In the Netherlands the "Gezondheidsraad" stressed the importance of an optimal use of antibiotics based on data obtained by regular surveillance of bacterial resistance patterns (6).
In 1988 a study was performed to analyse the availability of antibiotic formularies in different hospitals throughout the Netherlands. One of the conclusions was that the situation was not bad but could be better (7). In 1991 an update of the situation in the Netherlands has been performed, the results of this are presented here.

MATERIALS AND METHODS

In April-May 1991 Dutch hospitals (n=109) were asked to send their formulary as well as data available on antibiotic susceptibility patterns to the authors. In addition data on the use of the following groups of antimicrobial agents were collected by a questionnaire: aminoglycosides, aztreonam, co-trimoxazole, imipenem, second- and third-generation cephalosporins, co-amoxiclav, anti-pseudomonal penicillins, fluoroquinolones and vancomycin.
For the analysis of the data the hospitals were divided into three groups, group A: university hospitals, groep B: hospitals with more than 500 beds, group C: hospitals with less than 500 beds. The use of antibiotics was calculated as the defined daily doses (DDD) per 100 bed days. The DDD is defined as the assumed average dose per day for a drug of antimicrobial agent used for its main indication in adults (8). One has to keep in mind that the DDD is a technical unit of measurement which is independent of differences in price or in preparations. Therefore the DDD can only be used as an approximate estimate of antibiotic consumption. However, it is especially useful for comparisons between different hospitals or countries.
To correlate the data on the usage of antibiotics to the antibiotic guidelines, the DDD per 100 bed days per antibiotic were divided by the number of first-line indications for that particular compound.

The formularies were analysed in terms of year of publication, the authors and the type of guidelines the formulary set out. The availability of the antibiotic susceptibility patterns were reviewed per region, per hospital, per ward and per specimen.

RESULTS

Thirty-eight antibiotic formularies were received, which were used in 78 hospitals: six out of eight university hospitals, 21 out of 40 hospitals (53%) with 500 beds or more. If a region was served by more than one hospital, together consisting of more than 500 beds, the hospitals were classified as one hospital belonging to group B. From the 34 relatively small hospitals (less than 500 beds) 11 formularies (32%) were obtained. No formulary was available from 31 hospitals: 15 did not have the intention to set up guidelines for the use of antibiotics. Nine hospitals started up with their first formulary and seven were preparing an updated version of the existing one.
The year of publication of the formularies ranged from 1983 (n=1) to spring 1991 (n=1). Fifteen formularies dated from 1987 or earlier. All formulary committees consisted of a hospital pharmacist and a medical microbiologist complemented with clinicians (internal medicine 66%, surgery 44% and/or pediatrics 44%). Three of the formularies stated clearly that clinicians have to commit themselves to the advices given. Half of the formularies mentioned that the advices have to be considered as guidelines only. The others did not mention the purpose of the proposed guidelines.
The availability of susceptibility patterns of isolates to the hospitals participating in the survey ranged from no data at all (n=14) to extensive data per species, per material and per ward (n=5). Only limited data were available from the other hospitals. Moreover, these data were mostly derived from the region the hospital belongs to, and not from the hospital itself.
From 20 out of 78 hospitals data on antibiotic usage as well as on antibiotic guidelines were obtained. Several hospitals used the same formulary e.g. hospitals B1 and C1 shared one formulary and C2 and C3 shared another. A regional formulary was used by

hospitals B9, C4, C5 and C6. Therefore 15 different formularies were analyzed from 20 hospitals.
The most important indications mentioned in the antibiotic guidelines for the use of antimicrobial agents studied are shown in Table 1.

TABLE 1

MOST IMPORTANT INDICATIONS MENTIONED IN 15 FORMULARIES (N) FOR EACH GROUP OF ANTIMICROBIAL AGENTS

Group of antimicrobial agents	Indication	Mentioned in Formulary (n)
Aminoglycosides	Endocarditis	15
	Septicaemia	10-13
	Meningitis	10
	Pneumonia	7
Co-amoxiclav	Pneumonia	3
Antipseudomonal penicillins	Septicaemia	8
	Pneumonia	5
Aztreonam	Septicaemia	1
Cephalosporins		
second generation	Septicaemia	4-5
third generation	Septicaemia	4
	Pneumonia	3
	Meningitis	5-6
Co-trimoxazole	Pneumonia	10
	Prostatitis (acute)	10
	Dysentery	10
	Typhoid fever	3
Fluoroquinolones	Prostatis (acute)	2
	Typhoid fever	2
Imipenem	Granulocytopaenia	1
Macrolides	Pneumonia	9
	Gastroenteritis	14
	Tonsillitis	10
	Urethritis	2

All formularies recommended the use of aminoglycosides for the treatment of septicaemia. In 14 out of the 15 formularies macrolides were the drugs of choice for the treatment of *Legionella* pneumonia and *Campylobacter* gastroenteritis. In addition, ten formularies mentioned the same indications for

aminoglycosides and macrolides, i.e. meningitis and tonsillitis respectively. The use of co-trimoxazole for the treatment of pneumonia, *Shigella* dysentery and acute prostatitis was recommended with the same frequency. Only one university hospital mentioned an indication for the use of aztreonam and imipenem in its formulary. A limited indication for the use of fluoroquinolones i.e. acute prostatitis and typhoid fever was mentioned in only two formularies.
The usage of the antimicrobial agents in these hospitals is shown per hospital in table 2. Considerable differences were observed between hospitals of the three groups. Co-amoxiclav was the drug of choice in one university hospital (6.6 DDD per 100 bed days), whereas in the other group A hospitals it was hardly used. Also for the groups B and C hospitals a wide variation for some compounds was observed. The use of co-amoxiclav in group B hospitals ranged from zero to 4.4 DDD, in group C from zero to 18 DDD per 100 bed days. For the second generation cephalosporins a wide range in use was observed as well, i.e. for group B from 0.7 to 10 DDD and for the group C hospitals from 0.2 to 6 DDD per 100 bed days. The variation for the other compounds was distinctly less.
The ratio between the usage and the number of indications for which the different agents were the drug of choice is shown in Table 3. Remarkably, fluoroquinolones were used in all hospitals (Table 2) but were only mentioned in the formularies of six hospitals (Table 3).

DISCUSSION

The data in the present study demonstrate that the availability of antibiotic formularies and the adherence to of the recommendations given require further improvement in most Dutch hospitals. The statements of Barclay "Prescribing antibiotics: not entirely bad, but could be better" still applies for the Dutch situation in 1991 (9). In 1991 6/8 (75%) of the university hospitals and about half (i.e. 53%) of the hospitals with 500 beds or less had written guidelines. However 15 out of the 38 formularies dated from 1987 or earlier. Taken into account the rapid develop-

TABLE 2

ANTIBIOTIC USAGE IN 20 DUTCH HOSPITALS
Expressed in DDD per 100 bed days

Hospital	Antibiotic							
	Ami	Ctx	Cep	Cep	Aug	Mac	Pen	Qui
				2nd	3rd			
A								
1	1 8	4 0	2 6	2 1	2 0	2 0	1 0	4 1
2	2 9	4 5	2 4	1 8	0 6	0 9	0 4	2,4
3	3 6	4 3	1 6	1 4	6 6	1 2	0 6	4 5
B								
1	0 9	1 3	0 7	1 8	4 4	0 6	0 1	0 8
2	2 0	2 3	1 1	0 75	0 5	0 6	0 3	2 0
3	1 7	3 8	3 5	2 0	0 5	1 4	0 0	0 8
4	1 7	3 0	8 0	0 6	0 9	0 6	0 1	1 3
5	0 8	3 0	2 3	0 3	1 0	1 1	0 1	0 6
6	1 1	2 0	5 1	0 25	-	0 8	-	2 0
7	1 1	5 5	10	0 8	4 4	1 8	-	2 3
8	0 1	1 1	0 7	0 3	-	0 2	-	2 3
9	1 0	4 8	1 6	1 4	0 1	0 6	0 3	3 0
10	1 8	1 8	3 2	0 6	2 4	0 8	0 1	3 4
C								
1	0 0	2 7	0 3	1 7	4 4	0 0	0 0	2 5
2	1 8	1 7	0 2	0 1	18	0 7	0 1	0 4
3	2 6	2 0	0 2	0 2	14	0 2	0 1	0 4
4	0 6	5 7	1 0	0 7	-	1 3	0 3	3 0
5	0 7	1 7	2 4	0 29	-	0 4	-	2 1
6	1 2	1 0	2 4	0 10	1 6	1 5	0 1	0 7
7	0 3	1 7	6 0	1 8	5 5	0 26	0 10	2 8

Ami = aminoglyosides Ctx = co-trimoxazole Cep 2nd = second generation cephalosporins
Cep 3rd = third generation cephalosporins Aug = co-amoxiclav
Mac = macrolides Pen = antipseudomonal penicillins Qui = fluoroquinolones

TABLE 3

RATIO BETWEEN THE NUMBER OF DDD PER 100 BED DAYS AND THE NUMBER OF FIRST-LINE INDICATIONS, MULTIPLIED BY 100

Hospital	Antibiotic							
	Ami	Ctx	Cep 2nd	Cep 3rd	Aug	Mac	Pen	Qui
A								
1	10	80	180	34	200	67	-	33
2	22	113	120	90	-	30	-	17
3	21	61	-	28	55	30	450	12
B								
1	5	39	24	19	563	-	27	14
2	11	46	55	75	-	21	-	16
3	30	300	17	33	-	45	40	-
4	7	105	85	33	-	30	-	6
5	7	75	0	-	-	110	-	-
6	8	43	36	25	-	28	-	0
7	10	138	114	-	-	90	-	0
8	0.7	110	35	10	-	10	18	-
9	5	96	53	70	-	15	-	6
10	10	65	-	10	140	-	115	-
C								
1	0.2	74	12	15	563	-	83	4
2	8	15	2	12	252	22	-	7
3	11	18	2	16	194	7	-	7
4	3	114	33	35	-	33	-	6
5	4	34	80	15	-	10	-	0
6	6	54	54	22	-	38	-	21
7	2	32	140	117	-	19	-	32

\- antibiotic not mentioned in formulary
Abbreviations: see Table 2.

ment of new drugs in the past five years (e.g. fluoro-quinolones and macrolides) a revision of the formulary on a regular basis (every two to three years) is highly recommended. If no up-to-date formulary is used it is very likely that discrepancies between written guidelines and real usage do occur as observed in the present study. All twenty hospitals used fluoroquinolones, ranging from 0.4 to 4.5 DDD per 100 bed days, but fluoroquinolones were

mentioned in only six formularies. The main reason for this discrepancy is that the fluoroquinolones were introduced in the Netherlands from 1988 and later. Therefore, all formularies before that date did not include quinolones but the compounds were in use in 1991. Another remarkable discrepancy is the usage of co-amoxiclav by almost all hospitals, whereas the compound was only mentioned in seven formularies.
To our knowledge there is no generally accepted method to relate the overall use of antimicrobial agents to the guidelines laid down in the formularies. Therefore, arbitrarily, the ratio between usage of a compound and the times that it was recorded as the drug of choice was calculated. However, one has to take into account that the prevalences of the indications mentioned in the formularies are not at all similar. Therefore comparing the figures between the different groups of antimicrobial agents is unhelpful. However, one can compare ratio figures between hospitals within one group of agents. The wide variations observed in table 3 for almost all agents studied are obvious, although for aminoglycosides and the antipseudomonal penicillins the ratios were within a narrower range.
There are several reasons for the wide variation for the other agents in the different hospitals. One reason is the prophylactic use of a compound in surgery. The calculation of the ratio figures was based only on therapeutic indications and not prophylactic use. It is known that co-amoxiclav had been used as prophylactic agent in hospitals B1, B4, C1, C2 and C3 from 1989 (personal communications). The same is true for the use of second generation cephalosporins in hospital C7. A second reason is differences in the patient population of the various hospitals. Hospitals B1 and C1 used the same formulary. Hospital C1 is a low care hospital and as expected (table 2) there were lower ratios for aminoglycosides, second generation cephalosporins and antipseudomonal penicillins in hospital C1 than in hospital B1. However, the reverse was true for co-trimoxazole and the oral fluoroquinolones, whereas the ratio for co-amoxiclav was similar for both hospitals. Interesting data were also found for hospitals B4, C4, C5 and C6. All four hospitals shared the same formulary. Although hospital B4 is the largest, only for third generation cephalosporins was the

highest ratio observed in this hospital (70 compared to 35, 15 and 22 in the other hospitals). However, hospital C4 showed the highest ratio for co-trimoxazole, and for hospitals C4 and C6 it was for the macrolides. For the antipseudomonal penicillins hospital C6 showed the highest ratio and hospital C5 for the second generation cephalosporins. Thus, differences in patient population of the hospitals alone could not explain the wide variation in ratios (Table 3). Finally, one has to take into account that the wide variation might be due to discrepancies between actual usage and the recommendations given in the formularies. This is obviously the case for the fluoroquinolones. Other workers have also reported such inappropriate use (Table 4). Inappropriate use was usually defined as use not according to the guidelines of that hospital, administration of the agent without signs of an infection, incorrect dosage or inappropriate route of administration. In the studies cited in Table 4, inappropriate use ranged from 11% in a survey in 1971 up to 62% in a survey performed from 1967-1969 in seven community hospitals in the USA. The figures for England were hardly any better, the highest percentage of inappropriate use (50%) being found in a survey of treatment of urinary tract infections (15). Furthermore, analysis by service showed that in the medical departments inappropriate use was distinctly lower than in the surgical or gynaecological department (11, 19). In the Netherlands there has been one study comparing the choice of antibiotic therapy for the treatment of septicaemia with the guidelines of the formulary. Discrepancies were observed in 30% of all prescriptions (21).

Most of the studies concluded that a formulary alone is not sufficient to improve the use of antibiotics. Education is considered to be very important (22). Educational programmes might show some effect, but conflicting data do exist (23-25).

Continuing readily available consultation of the microbiologists and pharmacists is considered to be an effective method (26). Also higly recommended by the IDSA is periodic information for medical staff concerning antibiotic usage, as well as trends in antibiotic susceptibility patterns of the own hospital isolates (4).

Control of antibiotic usage will reduce antibiotic resistance and reduce costs (23, 27, 28). The IDSA stressed the importance that antibiotic formularies should be based on antibiotic susceptibility patterns of the own hospital isolates (4). These data include susceptibility pattern by ward, by specimen and by species. Only 5 of the 78 Dutch hospitals participating in the study had these data readily available. Two-thirds of the hospitals were able to provide data on susceptibility patterns of isolates from the region the hospital belongs to but not from the hospital itself.

TABLE 4

INAPPROPRIATE USE OF ANTIMICROBIAL AGENTS IN DIFFERENT SURVEYS

References	year of survey	inappropriate use (%)
10	1952-1956	52
11	1967-1969	62
12	1975	41
13	1978	22
14	1971	11
	1979	20
15-17	1978	40-50
18	1980	14
19	1980	2
20	1979	28
	1980	35
21	1987	30

Although the present study did not include all Dutch hospitals, it is not very likely that the hospitals participating in the study are unrepresentative of the situation in Dutch hospitals in general. Furthermore, it is to be expected that the implementation of computarized data management systems in many microbiological laboratories will in due course improve the availability of (extensive) antibiotic susceptibility patterns.

The data in the present study underscore the need for an active collaborative approach between medical staff, hospital pharmacy and microbiological laboratory (29, 30) in order to maintain a relatively low level of antibiotic resistance in Dutch hospitals (31).

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CHAPTER III

ANTIMICROBIAL DRUG USE IN HOSPITALS IN THE NETHERLANDS, GERMANY AND BELGIUM

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SUMMARY

Data on the use of antimicrobial drugs was collected by means of an inquiry to 30 hospitals in Belgium (15 in Dutch sector and 15 in the French sector), 21 hospitals in Germany and 20 hospitals in the Netherlands. The use of these drugs was expressed as the number of defined daily doses (DDD) per 100 bed days by the anatomical therapeutical chemical classification system. The total use of antimicrobial agents was significantly ($p < 0.001$) higher in both parts of Belgium (55.6 and 52.0 DDD per 100 bed days) than in Germany (37.9 DDD per 100 bed days) or the Netherlands (34.1 DDD per 100 bed days). In particular co-amoxiclav, the first and second generation cephalosporins, aminoglycosides and fluoroquinolones were used more in Belgium than in either of the other countries. At least part of the differences observed in antimicrobial drug use could be explained by differences in written antibiotic policy.

INTRODUCTION

There is worldwide concern about the increased bacterial resistance to various antimicrobial agents, including resistance to recently introduced compounds (1). It is widely accepted that this increased resistance is mainly due to the use of antibiotics (2). Moreover, the correlation between the prevalence of multiple resistant microorganisms and the total use of broad-spectrum antibiotics (e.g. cephalosporins) has been documented (3). Variations in levels of resistance between different countries and between hospitals have been demonstrated (4, 5). Distinct differences in resistance to various beta-lactam compounds of Gram-negative blood culture rods isolated from hospitals in Germany, Belgium and the Netherlands have been described by the European Study Group on Antimicrobial Resistance (6).
Unfortunately, only limited data on the total use of antimicrobial agents in hospitals in various countries are available. Martini et al. (7) studied the use of these drugs in ten hospitals in Italy, seven in Portugal and nine in Spain. Data on antimicrobial drug use in northern Europe are scarce and usually limited to that from

university hospitals (8) or from only small numbers of hospitals (9), which may not be representative of the use of these drugs in other hospitals.
In a multi-regional European project, antimicrobial drug use in hospitals in the Netherlands, Belgium and Germany (Nordrhein Westfalen) was studied. In addition, an attempt was made to relate the usage of antibiotics to the levels of antibiotic resistance in these three countries.

MATERIALS AND METHODS

Data on the use of antimicrobial agents in hospitals in Belgium, the Netherlands and Germany (state of Nordrhein Westfalen) were collected by means of a written inquiry distributed to hospital pharmacists in these countries in the year 1990. A total of 30 Belgian hospitals (15 from Dutch sectors of Belgium and 15 from French sectors), 20 Dutch hospitals and 21 German hospitals participated in the survey. The use of antimicrobial agents was expressed as the number of defined daily dosages (DDD) per 100 bed days for the anatomical therapeutical chemical (ATC)-subclasses G04A (urinary antiseptics) and J01 (systemic antibacterial agents). The cephalosporins were divided into three generations. The first generation consisted of cephadroxil, cephalexin, cefaclor, cefradine, cephalothin, cefazolin and cephaloridine. The second generation consisted of cefamandole, cefuroxime and cefoxitin, whereas all others were classified as third generation cephalosporins.
The number of beds, the number of hospitalisation days and the number of admissions in 1990 were recorded for each hospital. The number of bed days was obtained by subtracting the number of admissions from the total number of hospitalisation days. The duration of hospitalisation was obtained by dividing the total number of hospitalisation days by the number of admissions.
All drugs available in (at least one of) the three countries were specified by trade name, generic name, strength and mode of administration (injection or oral). The specified use of each dosage form was recorded in the survey. The sources of available preparations used were as follows: "Rote Liste 1991" (Germany),

Repertoire commente des medicaments 1991 (Belgium) and Repertorium 1991 (The Netherlands). The use of norfloxacin was scored separately from the other fluoroquinolones because norfloxacin is used only for urinary tract infections, whereas the other fluoroquinolones are also used for other indications.
Statistical analysis of the data was performed by Student's t-test (10, 11).

RESULTS

The number of hospitals, hospital beds and bed days and the duration of hospitalisation in the three countries are shown in Table 1.

TABLE 1

CHARACTERISTICS OF THE HOSPITALS PARTICIPATING IN THE SURVEY

Characteristic	Belgium Dutch sector	French sector	Germany	The Netherlands
Mean no of beds (range)	510 (125-1675)	313 (84-906)	720 (230-1907)	550 (120-1249)
Mean no of bed days in thousands (range)	140 (37.0-400)	88 9 (24 0-259 2)	196 (67 0-530)	141 (29 7-350)
Mean duration of hospitalisation in days (range)	11 13 (7 86-16 62)	10 34 (6 30-13 29)	12 17 (8 19-15 70)	10 63 (7 32-12.76)
No of university hospitals/total	3/15	2/15	2/21	2/20

The number of hospital beds was significantly lower in the French sector of Belgium than in Germany ($p < 0.001$) or in the Netherlands ($p < 0.02$). The number of bed days was also lower in the French sector of Belgium in comparison with Germany ($p < 0.001$) or the Netherlands ($p < 0.05$). The duration of hospitalisation was longer in Germany than in the Netherlands (p

< 0.01) or the French sector of Belgium ($p < 0.05$). The number of university hospitals was similar in the study groups.
The use of the antimicrobial agents in the three countries, expressed as DDD/100 bed days for each ATC subclass, is shown in Table 2. The combined data on the use of penicillins, cephalosporins, total beta-lactam antibiotics and total fluoroquinolones are given in Table 3. Significant differences in the use of almost all compounds were observed between both parts of Belgium and the use in Germany and the Netherlands. The statistical significance of the differences observed is summarized in Table 4. Table 5 shows the use of each group of antimicrobial agents as a percentage of total antimicrobial drug use in each country.
The total use of antimicrobial drugs was significantly higher in hospitals in both parts of Belgium in comparison with that in Germany or the Netherlands ($p < 0.001$). The differences observed are mainly due to differences in the use of co-amoxiclav, first and second generation cephalosporins, aminoglycosides and total fluoroquinolones (i.e. norfloxacin and other fluoroquinolones). In contrast, only marginal differences in use were observed between the hospitals in the French and Dutch sectors of Belgium. Significant differences were found only in the use of second generation cephalosporins and macrolides (Tables 2 and 4).
The use of narrow-spectrum penicillinase-sensitive penicillins such as benzylpenicillin was higher in Germany than in either of the other two countries. The same was true for the use of antipseudomonal penicillins such as azlocillin and piperacillin. In contrast, in Germany the use of co-amoxiclav was lower than in Belgium and the Netherlands, although the difference between Germany and the Netherlands did not reach statistical significance (Tables 2 and 4).
Different patterns in cephalosporin use were observed in the three countries. In Belgium, the total use of cephalosporins was significantly higher in comparison with Germany and the Netherlands (Tables 3 and 4). Differences in the use of second and third generation cephalosporins in the three countries were observed as well. The use of second generation cephalosporins (mostly cefuroxime) was approximately tenfold lower in Germany

compared to Belgium. In contrast, in Germany the use of third generation cephalosporins was almost twice as high as in Belgium and fourfold higher than in the Netherlands.

Monobactams and carbapenems are used to a very limited extent in the three countries, although the range in their use was relatively wide. In some Belgian university hospitals a relatively high use of aztreonam (1.41 DDD/bed days) and imipenem/cilastatin (0.80 DDD/100 bed days) was observed.

Vancomycin is used more frequently in Belgium than in the two other countries, although only the difference between the Netherlands and the Dutch sector of Belgium reached statistical significance.

TABLE 2

ANTIMICROBIAL DRUG USE IN DEFINED DAILY DOSAGES PER 100 BED DAYS ± STANDARD DEVIATION (RANGE)

Group	Belgium Dutch sector	 French sector	Germany	The Netherlands
Tetracyclines	3 43 ± 2 38	1 94 ± 1 32	4 12 ± 2 53	2 18 ± 1 51
	(0 89 - 8 56)	(0 05 - 4 57)	(0 93 - 9 45)	(0 21 - 7 06)
Chloramphenicol/	0 32 ± 0 90	0 08 ± 0 11	0 02 ± 0 02	0 04 ± 0 06
thiamphenicol	(0 - 3 78)	(0 - 0 39)	(0 - 0 09)	(0 - 0 20)
Ampicillins	5 85 ± 3 43	5 63 ± 3 98	6 54 ± 3 71	8 24 ± 3 89
	(1 35 - 11 6)	(0 89 - 16 4)	(1 21 - 14 8)	(2 58 - 19 6)
Ureido-penicillins	0 55 ± 0 48	0 76 ± 0 56	1 39 ± 0 89	0 13 ± 0 17
	(0 08 - 2 08)	(0 23 - 1 94)	(0 - 3 60)	(0 - 0 72)
Penicillins	1 76 ± 1 27	1 33 ± 1 65	4 88 ± 3 29	1 97 ± 1 48
(penicillinase sens)	(0 05 - 4 06)	(0 - 6 02)	(1 37 - 12 8)	(0 37 - 4 83)
Penicillins	2 60 ± 1 71	1 79 ± 1 13	1 08 ± 0 81	2 64 ± 1 52
(penicillinase res)	(0 69 - 6 25)	(0 12 - 3 79)	(0 08 - 2 86)	(0 69 - 6 08)
Clavulanate	11 9 ± 5 38	11 6 ± 5 48	1 53 ± 1 91	3 50 ± 5 56
penicillin-comb	(0 - 22 9)	(0 23 - 19 4)	(0 - 6 53)	(0 05 - 22 1)
1st generation	5 76 ± 5 30	7 16 ± 2 54	2 76 ± 2 75	1 17 ± 1 76
cephalosporins	(1 02 - 21 1)	(3 05 - 11 5)	(0 - 10 8)	(0 - 5 97)
2nd generation	7 08 ± 4 70	5 42 ± 3 19	0 66 ± 0 80	3 38 ± 2 48
cephalosporins	(1 26 - 18 1)	(2 06 - 12 4)	(0 - 2 20)	(0 09 - 9 59)
3rd generation	3 00 ± 3 22	2 46 ± 1 67	4 96 ± 3 44	1 12 ± 0 82
cephalosporins	(0 33 - 11 9)	(0 16 - 5 34)	(0 74 - 10 3)	(0 07 - 2 41)
Monobactams	0 18 ± 0 30	0 27 ± 0 20	0 00 ± 0 01	0 04 ± 0 12
	(0 - 1 41)	(0 - 0 69)	(0 - 0 02)	(0 - 0 42)
Carbapenems	0 18 ± 0 22	0 20 ± 0 21	0 13 ± 0 10	0 10 ± 0 12
	(0 - 0 74)	(0 - 0 80)	(0 - 0 31)	(0 - 0 36)
Trimethoprim	0 04 ± 0 07	0 01 ± 0 02	0	0 17 ± 0 45
	(0 - 0 25)	(0 - 0 10)	(0)	(0 - 1 64)

TABLE 2 (continued)

ANTIMICROBIAL DRUG USE IN DEFINED DAILY DOSAGES PER 100 BED DAYS ± STANDARD DEVIATION (RANGE)

Group	Belgium		Germany	The Netherlands
	Dutch sector	French sector		
Co-trimoxazole	2 67 ± 1 57 (1 31 - 5 53)	2 14 ± 1 41 (0 25 - 5 26)	3 97 ± 2 08 (0 - 8 49)	3 13 ± 0 91 (1 51 - 4 72)
Macrolides	1 04 ± 0 55 (0 39 - 2 47	2 16 ± 1 59 (0 26 - 5 70)	0 85 ± 0 77 (0 10 - 2 73)	1 12 ± 0 48 (0 31 - 2 36
Lincomycins	0 22 ± 0 17 (0 - 0 64)	0 33 ± 0 41 (0 - 1 67)	0 37 ± 0 33 (0 04 - 1 04)	0 19 ± 0 26 (0 - 1 14)
Aminoglycosides	2 42 ± 1 01 (1 15 - 4 93)	2 51 ± 1 14 (0 83 - 4 71)	1 06 ± 0 74 (0 10 - 3 31)	1 34 ± 0 93 (0 03 - 3 94)
Fluoroquinolones	2 23 ± 1 50 (0 07 ± 4 73)	1 65 ± 1 31 (0 - 4 59)	2 14 ± 1 55 (0 70 - 5 96)	0 75 ± 0 63 (0 03 - 2 11)
Norfloxacin	1 84 ± 1 06 (0 16 - 4 04)	2 08 ± 1 50 (0 - 5 08)	0 22 ± 0 44 (0 - 1 68)	0 69 + 0 61 (0 - 2 39)
Vancomycin	0 33 ± 0 43 (0 - 1 49)	0 25 ± 0 43 (0 03 - 1 62)	0 10 ± 0 17 (0 - 0 65)	0 07 ± 0 13 (0 - 0 52)
Metronidazole	1 45 ± 0 97 (0 - 3 61)	1 17 ± 0 64 (0 26 - 2 31)	0 71 ± 0 41 (0 - 1 98)	1 00 ± 0 90 (0 - 1 75)
Anticystitis drugs	0 65 ± 0 78 (0 - 2 36)	0 86 ± 0 81 (0 - 1 94)	0 29 ± 0 90 (0 - 4 15)	0 96 ± 1 00 (0 - 3 22)
Total	**55.6 ± 9.99 (38.6 - 70.0)**	**52.0 ± 12.7 (32.6 - 81.4)**	**37.9 ± 7.09 (27.5 - 55.4)**	**34.1 ± 6.98 (23.0 - 46.6)**

TABLE 3

ANTIMICROBIAL DRUG-GROUP USE IN DEFINED DAILY DOSAGES PER 100 BED DAYS (STANDARD DEVIATION)

Drug group	Belgium		Germany	The Netherlands
	Dutch sector	French sector		
Penicillins	22 7 (7 25)	21 1 (7 99)	15 4 (5 35)	16 7 (5 99)
Cephalosporins	15 7 (6 71)	15 1 (5 11)	8 39 (3 35)	5 68 (2 95)
Total beta-lactam agents	38 9 (7 65)	36 7 (11 3)	24 1 (5 48)	22 5 (6 41)
Fluoroquinolones	4 08 (2 00)	3 73 (1 67)	2 36 (1 50)	1 44 (0 88)

TABLE 4

SIGNIFICANT DIFFERENCES IN ANTIMICROBIAL DRUG USE BETWEEN THE COUNTRIES PARTICIPATING IN THE SURVEY

Drug group	B-F D	B-F NL	B-NL D	B-NL NL	D NL
Tetracyclines	< 0 01				< 0 01
Ureido-penicillins	< 0 02	< 0 001	< 0 001	< 0 01	< 0 001
Penicillins (penicillinase sensitive)	< 0 001		< 0 001		< 0 001
Penicillins (Penicillinase resistant)	< 0 005	< 0.05	< 0 01		< 0 001
Clavulanate/sulbactam penicillin combinations	< 0 001	< 0 001	< 0 001	< 0 001	
1st generation cephalosporins	< 0 001	< 0 001		< 0 01	< 0 05
2nd generation cephalosporins	< 0.001	< 0 05	< 0.01		< 0 001
3rd generation cephalosporins	< 0 001	< 0 01		< 0 05	< 0 001
Aztreonam	< 0.001				< 0 001
Co-trimoxazole	< 0 01	< 0 05	< 0 05		
Macrolides	< 0 01	< 0 02			
Lincomycins					< 0 05
Aminoglycosides	< 0 001	< 0 01	< 0 001	< 0 001	
Fluoroquinolones		< 0 02		< 0 01	< 0 001
Norfloxacin	< 0 001	< 0 001	< 0 001	< 0 001	< 0 01
Vancomycin				< 0 05	
Metronidazole	< 0.05		< 0 01		
Anticystitis drugs	< 0 05				< 0 05
Penicillins	< 0 05		< 0 01	< 0 02	
Cephalosporins	< 0 001	< 0 001	< 0 001	< 0 001	< 0 01
Total beta-lactam agents	< 0 001	< 0 001	< 0 001	< 0 001	
Total fluoroquionolones	< 0 02	< 0 001	< 0 01	< 0 001	< 0 05
Total	< 0 001	< 0 001	< 0 001	< 0 001	

B-F French speaking part of Belgium
B-NL Dutch speaking part of Belgium
D Germany
NL The Netherlands

TABLE 5

USE OF VARIOUS GROUPS OF ANTIMICROBIAL AGENTS AS A PERCENTAGE OF TOTAL ANTIMICROBIAL DRUG USE IN THE COUNTRIES PARTICIPATING IN THE SURVEY

Drug group	Belgium French sector	Dutch sector	The Netherlands	Germany
Penicillins	40 6	40 8	48 9	40 8
Cephalosporins	28 9	28 2	16 7	22 1
Beta-lactam agents	70 5	70 0	66 1	63 7
Tetracyclines	3 7	6 2	6 4	10 9
Aminoglycosides	4 8	4 4	3 9	2 8
Quinolones	7 2	7 3	4 2	6 2
Macrolides	4 2	1 8	3 3	2 2
Co-trimoxazole	4 1	4 8	9 2	10 5
Metronidazole	2 2	2 6	2 9	1 9
Others	3 3	2 9	4 0	1 8
Total	**100**	**100**	**100**	**100**

DISCUSSION

In the present study, the consumption of antimicrobial drugs was expressed as the number of DDD per 100 bed days, which is a very useful method for comparative studies of drug utilisation in different hospitals (12). The classification of drugs is commonly performed according to the ATC system. This is an internationally used classification system, monitored by the WHO Collaboratoring Centre for Drug Statistics Methodology in Oslo, Norway (13). Data on drug use expressed as DDD per 100 bed days and classified according to the ATC code which are obtained in one country are therefore directly comparable to the data from other countries.

It was not possible to explain all the differences observed in antimicrobial drug use in both parts of Belgium, Germany and the Netherlands, because no studies comparing the antimicrobial drug policy in hospitals in the three countries have been published thus far.

In the Netherlands, most hospitals have written antibiotic formularies, specific for that hospital or a group of collaborating hospitals.
In Belgium most hospitals use the Belgian edition of J.P. Sanford's Guide to Antimicrobial Therapy (14). This guide is of American origin and adapted to the Belgian situation in close cooperation with representatives and opinionleaders from university and other hospitals throughout the country. If this guide was followed closely in all Belgian hospitals, a relatively low standard deviation should be found in the use of various (groups of) antimicrobial drugs in comparison with use in the Netherlands, where most hospitals have composed their own antibiotic formularies. This was not observed in our study, however (Tables 2 and 3).
In Germany, most hospitals have their own antibiotic policies, but written antibiotic formularies are hardly available and are usually confined to a listing of the antibiotics which are in use in the hospital in question, without giving specific guidelines for each infection (W. Brandenburg, personal communication). Although written antibiotic formularies in the Netherlands are much more common than in Germany, it is surprising that the total use of antibiotics in Germany and the Netherlands is similar.
In the Belgium formulary (Sanford), co-amoxiclav is recommended as the drug of choice in sinusitis, otitis media, acute exacerbations of chronic bronchitis, pelvic inflammatory disease, cholangitis and pyelonephritis. The indications for its use in respiratory tract infections in the Netherlands are much more limited. In 30 antibiotic formularies from Dutch hospitals, co-amoxiclav was advised in only four formularies for acutely exacerbated obstructive lung disease, in three formularies for acute sinusitis and in four formularies for otitis media.
Most formularies contain no clear guidelines for duration of treatment with co-amoxiclav. Thus the different indications for this drug may contribute to its more frequent use in Belgian hospitals. The prevalence of beta-lactamase producing *Haemophilus influenzae* (often involved in respiratory tract infections) is higher in Belgium than in the Netherlands or Germany, which justifies its use in respiratory tract infections in Belgium.

First generation cephalosporins are indicated in Belgium as a first-line agent in pyelonephritis and sepsis and as a second-line agent in otitis media, cholangitis and sinusitis. In the Netherlands, the use of these drugs is usually limited to antibiotic prophylaxis in surgery.
The fluoroquinolones are used in Belgium for the treatment of prostatitis, gonorrhea, pyelonephritis and hospital-acquired pneumonia (14). These drugs were not mentioned in most Dutch formularies, mainly because 14 of the 30 formularies were dated 1988 or earlier, while ciprofloxacin was first introduced on the Dutch market in the second half of 1988. Only six of the 30 Dutch formularies mention the use of fluoroquinolones for acute pyelonephritis, whereas fluoroquinolones are indicated for acute prostatitis in 15 out of 30 formularies.
At least part of the differences observed in the use of co-amoxiclav, first generation cephalosporins and fluoroquinolones may therefore be explained by different indications for these drugs.
Another important factor influencing the use of antibiotics is the decision whether an infection should be treated with antibiotics and if so, how long treatment should last. Most formularies did not mention any data on these important criteria.
Cultural differences may play a very important role in the use of antibiotics. The use of antimicrobial drugs is much higher in the U.S.A. than in Germany, because of different approaches to the treatment of infections in both countries. In Germany most doctors are reluctant to prescribe antibiotics for mild infections, whereas in the U.S.A. the "fear of microbes" results in a high rate of prescription of antibiotics (15). No data from such "cultural" aspects of antibiotic policy are available from the Netherlands and Belgium.
The size of the hospital and the number of beds for intensive care treatment may also influence the use of antimicrobial agents. In an earlier study a significantly higher use of antimicrobial drugs was observed in Dutch university hospitals in comparison with non-university hospitals, regardless of the number of beds in these hospitals (16). In the present study the use of antimicrobial agents in three university hospitals was 41.3 - 70.0 DDD per 100 bed

days in the Dutch sector of Belgium, 32.6 and 66.7 in two university hospitals in the French sector of Belgium, 51.6 and 55.4 in the two German university hospitals, and 44.3 and 46.6 in the university hospitals in the Netherlands. The average use of antimicrobial agents in university hospitals was therefore higher than that in the other hospitals in Germany and in the Netherlands, but not in Belgium. It must be borne in mind that some Belgian hospitals are called "university hospitals" although only a few beds (sometimes <10%) have the status of "university beds". This may explain the relatively wide variation in antimicrobial drug use in Belgian university hospitals (M. Caprasse, personal communication). As the number of university hospitals was comparable in the four study groups, this could not explain the differences observed in antimicrobial drug use. Hekster and Barrett (9) have compared the use of antimicrobial drugs in nine university hospitals and 14 non-university hospitals in eight European countries. The use of parenteral cephalosporins was higher in the university hospitals (6-8 DDD/100 bed days) than in the other hospitals (3.0 DDD/100 bed days).

The total use of antimicrobial drugs in the Dutch hospitals in our survey is comparable to that observed in four Dutch university hospitals in 1985 - 1986. Schuitenmaker and Versluis (8) found a total use of 36 - 52 DDD/100 bed days in these hospitals. They also found relatively low use of 29 DDD/100 bed days in a Belgian university hospital. This low use of antimicrobial drugs in Belgium was not confirmed by our study. The authors found a total use of 43 and 62 DDD/100 bed days in two Swedish university hospitals. Few detailed data from other countries exist.

In a study performed in 1987, Martini and coworkers (7) found a high total average antimicrobial drug consumption in three Mediterranean countries: 58.6 (range 33.8 - 69.5) in ten Italian hospitals, 89.7 (range 38.8 - 149.2) in seven Portuguese hospitals and 83.5 (range 57.4 - 109.5) in nine Spanish hospitals (7). The antimicrobial drug use in Italy was comparable to that found in the present study in Belgium. The total use of cephalosporins in their study (10.7 - 13.6 DDD/100 bed days) was comparable to our data from Belgium. The use of aminoglycosides (3.5; 6.9 and 9.3 DDD/100 bed days in Italy, Portugal and Spain respectively) was much higher than that observed in Belgium, Germany and the Netherlands in the present study. One has to consider that the data from the Mediterranean study were collected three years before our study, so it is not possible to make a direct comparison of the data from the two studies.

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CHAPTER IV

ANTIBIOTIC POLICY IN DUTCH HOSPITALS
The treatment of bacterial bronchitis

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Submitted for publication

ABSTRACT

Guidelines for therapy in bacterial bronchitis from 41 antibiotic formularies in use in 91 Dutch hospitals were analysed. The classification of bronchitis and the terminology used were highly variable and were not clearly defined in many cases. Most formularies made no statements about the indication for antibiotic treatment of bacterial bronchitis. Only a few formularies emphasized the importance of adequate assessment and treatment of the underlying pulmonary disease, such as a chronic obstructive pulmonary disease. In view of the low percentage of antibiotic resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* in the Netherlands, amoxycillin, doxycycline and co-trimoxazole are still agents of first choice in the treatment of bacterial bronchitis. Most of the formularies did not comment on the duration of treatment. Very few studies have been performed that investigate adequate dosage and duration of therapy for bacterial bronchitis. Based on the results of this analysis, recommendations are made for a more adequate formulary advice in bacterial bronchitis.

INTRODUCTION

Most Dutch hospitals have created antibiotic formularies, with guidelines for antimicrobial therapy which are specific for one hospital or for a group of collaborating hospitals in the same region (1).

Respiratory tract infections are quantitatively the most important indications for antimicrobial agents, both in general practice and in hospitals. As there are important differences in the antibiotic requirements in the treatment of upper and lower respiratory tract infections and between bacterial bronchitis and pneumonia, we will focus on the therapy recommendations in Dutch antibiotic formularies for bacterial bronchitis.

METHODS

By means of a written request to members of the Dutch As-

sociation of Hospital Pharmacists (NVZA), we have collected antibiotic formularies from hospitals from all over the country. Only those hospitals were included in the survey, that included bronchitis in these formularies. The following aspects of the antibiotic formularies were recorded:
- the terminology
- division of bacterial bronchitis into subcategories
- the choice, dosage and duration of antibiotic therapy
- general guidelines and advice concerning diagnosis and intervention strategies in lower respiratory tract infections.

RESULTS

Materials

We received a total of 43 antibiotic formularies. One formulary was excluded, because it was too old (1983) to be a reliable guide for antimicrobial therapy and one formulary did not contain a chapter on bacterial bronchitis. Forty-one formularies used in 91 Dutch hospitals, including 6 university hospitals, were analysed.
The year of publication of these formularies was as follows:

1985	1
1986	1
1987	3
1988	1
1989	3
1990	7
1991	9
1992	10
1993	6

Terminology

As shown in Table 1, the terminology for description of the type of bronchial infection was highly variable. A definition of the terms used was lacking in all formularies.
Lower respiratory tract infections were divided into bronchitis and pneumonia in 39 out of 41 formularies. In the other 2 formularies

no distinction between pneumonia and bronchitis was made and only general guidelines for the treatment of lower respiratory tract infections were given. Thirty-two formularies made a distinction between *acute bronchitis* and *acute exacerbations of chronic obstructive pulmonary disease* (COPD).

TABLE 1

TERMINOLOGY USED FOR DESCRIPTION OF BACTERIAL BRONCHITIS IN DUTCH ANTIBIOTIC FORMULARIES
The numbers correspond with the number of formularies in which the term is used.

Acute bronchitis	30
Exacerbation of chronic bronchitis	19
Acute exacerbation of chronic bronchitis	7
Exacerbation of COPD	5
Bronchitis	2
Chronic bronchitis or emphysema	2
Bacterial bronchitis	2
Acute bacterial bronchitis	1
Acute bronchitis (exacerbation)	1
Uncomplicated acute bronchitis	1
Acute exacerbation of COPD	1
Chronic asthmatic bronchitis and bronchiectasis	1
Acute tracheobronchitis	1
Chronic bronchitis and/or emphysema with purulent sputum	1

Diagnostic aspects

Twenty-two formularies gave no guidelines for a distinction between bacterial bronchitis and viral bronchitis, although some formularies stated that *acute bronchitis* was usually of viral origin. Four formularies strongly recommended the collection of bronchial secretion to support the proposed bacterial infection. A Gram-stain of the sputum or culture was recommended by 17 formularies. Three formularies stressed the importance to distinguish colonisation from infection, but did not mention criteria. One formulary stated that the mere presence of (especially Gram-negative) bacteria in the sputum was not an indication for antibacterial therapy and advised interpreting the microbiological data in a clinical context. One formulary recommended a throrough physical examination to distinguish *acute infection* from an *exacerbation of chronic infection.*

Therapy recommendations

The differentiation between *acute bronchitis* and *acute exacerbations of chronic bronchitis* had little impact on the therapy guidelines in the formularies. The guidelines for both "types" of bronchitis were similar in 27 of 32 formularies (84%) in which this distinction was made and different in five formularies. Culture results (specified per hospital ward) and clinical or outpatient samples, were presented by only one formulary.

Eight formularies specified guidelines for the treatment of *bronchitis* caused by either *Streptococcus pneumoniae, Haemophilus influenzae* or *Moraxella catarrhalis.* Two formularies also specified *Mycoplasma pneumoniae* as a possible causative organism.

Most formularies presented guidelines for the treatment of (presumed bacterial) bronchitis with (as yet) unknown pathogens, as shown in Table 2.

TABLE 2

ANTIMICROBIAL AGENTS USED IN THE TREATMENT OF BACTERIAL BRONCHITIS IN DUTCH ANTIBIOTIC FORMULARIES.
The numbers correspond with the number of formularies in which the antibiotic is used.

	First choice	Second choice	Third choice
Amoxycillin	29	4	3
Doxycycline	9	13	2
Co-trimoxazole	7	5	13
Co-amoxiclav	3	1	
Benzylpenicillin	1	1	
Erythromycin	2	1	1
Cefuroxime		2	
Trimethoprim			1

Some formularies used amoxycillin, doxycycline and/or cotrimoxazole as equal alternatives for the treatment of bacterial bronchitis, but most formularies specified drugs of first, second or third choice for the treatment of infections. Motivation for this follow-order was lacking in all but one of the formularies.
Four formularies did not recommend any specific antimicrobial drug, but mentioned that therapy must be based on culture results.
Therapy recommendations for betalactamase-producing *H.influenzae* or *M.catarrhalis* were given in 14 formularies (Table 3).

TABLE 3

RECOMMENDED DRUGS FOR THE TREATMENT OF BRONCHITIS CAUSED BY BETALACTAMASE-PRODUCING *H.INFLUENZAE* OR *M.CATARRHALIS*.
The numbers correspond with the number of formularies in which the antibiotic is used.

Co-amoxiclav	8
Co-amoxiclav or doxycyline or co-trimoxazole	3
Doxycycline or erythromycin	1
Doxycycline or co-trimoxazole or erythromycin	1
Cefuroxime or co-trimoxazole	1

One formulary recommended amoxycillin as the drug of choice in *acute bronchitis* and co-amoxiclav as the drug of choice in *exacerbations of chronic bronchitis.*
Guidelines for the long-term treatment of *chronic bronchitis* were given in 5 formularies. Co-trimoxazole (dose 480 mg twice daily), doxycyline (100 mg once daily) and amoxycillin (375 mg 3 times daily) were the drugs of choice for this indication, but most formularies did recommend against their long-term use in chronic bronchitis.

Dosage

The dosages suggested for amoxycillin and doxycycline are presented in Table 4. The vast majority of all formularies recommended for amoxycillin a dosage of 750 mg 3 times daily for the treatment of bacterial bronchitis, whereas a variety of other dosages was found in a few formularies. The dose recommenda-

tions for doxycyline were also similar in most formularies: 200 mg on the first day, followed by 100 mg once daily thereafter. The dose recommendations for co-trimoxazole were also completely uniform: 960 mg twice daily in all formularies that included this drug for the treatment of bacterial bronchitis. Although the usual dose for co-amoxiclav was 625 mg 3 times daily, one formulary recommended a dose of 1250 mg 3 times daily. Erythromycin was used in some formularies in case of penicillin allergy. The daily dosage was 2 g in all formularies, divided into 2-4 doses.
Recently introduced antibiotics such as fluoroquinolones, new macrolides, azalides or third generation oral cephalosporins were not recommended in any formulary.

TABLE 4

DOSE RECOMMENDATIONS FOR AMOXYCILLIN AND DOXYCYCLINE IN ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS.
The numbers correspond with the number of formularies in which the antibiotic is used.

Amoxycillin	
750 mg 3 times daily	27
375-750 mg 4 times daily	2
375-750 mg 3 times daily	1
375 mg 3-4 times daily	1
375 mg 3 times daily	1
500 mg 4 times daily	1
1000 mg 4 times daily	1
750 mg twice daily	1
750-1000 mg 3 times daily	1
Doxycycline	
200 mg qd first day, followed by 100 mg once daily	21
200 mg once daily	2
100 mg twice daily	2

Treatment duration
Data on the optimal duration of treatment were presented in only 12 formularies. The recommendations were as follows:

- 5 days	1 formulary
- 7 days	3 formularies
- 7-10 days	2 formularies
- 10 days	6 formularies

One formulary mentioned different guidelines for the duration of treatment for acute bronchitis (5-7 days) and obstructive pulmonary disease (at least 10 days). Another formulary did not give clear guidelines but stressed the importance of the clinical course.

General comments in the formularies
General remarks concerning diagnosis or the necessity of giving antibiotics in the treatment of bacterial bronchitis were absent in 24 formularies (59%). The comments in the other formularies varied from very short to extensive. Ten formularies stated that acute bronchitis without underlying pulmonary disease is almost always of viral origin and that this infection should only be treated with antibiotics after confirmation of a secondary bacterial infection.
The comments concerning "exacerbations of COPD" were quite variable. Five formularies stated that not only acute bronchitis, but also exacerbations of chronic bronchitis are usually of viral origin. One formulary concluded that antibiotics for the treatment of bronchitis are often useless and even harmful. Several other formularies stressed that antibiotics should be given only "if needed", without presenting clear criteria for the decision when to treat bronchitis with antibiotics.
Although two formularies mentioned that acute exacerbations are of viral origin in 75% of all cases, antibiotics should be started as soon as possible. Unfortunately the reasons for antimicrobial therapy were not specified (prevention of secondary bacterial infection?). One formulary recommended conservative treatment of an exacerbation without antibiotics. Another formulary specified

the indications for antimicrobial treatment of bacterial bronchitis: the patient must have at least two of the following three symptoms: fever, purulent sputum and dyspnoea.
Four formularies did not support maintenance treatment of chronic bronchitis with antibiotics and recommended that only exacerbations should be treated with antibiotics. Seven formularies presented guidelines for prophylactic use of antibiotics in chronic bronchitis, and three of these specified that this was only indicated in a very limited number of cases. Five formularies stated that repeated or long-term use of antibiotics in chronic bronchitis may result in changes of the bacterial flora and bring about the selection of resistant strains.
One formulary stressed attention to predisposing factors, such as underlying pulmonary disease or the presence of foreign bodies. The use of bronchodilators or inhaled corticosteroids in acute exacerbations of COPD was not discussed in the comments of any of the antimicrobial formularies.

DISCUSSION

Antibiotic policies for the treatment of bronchitis have been debated for many years. In determining the place of different antibiotics in lower respiratory tract infections, one is confronted with several problems: the terminology used, the diagnosis of bacterial bronchitis and the contribution of antimicrobial therapy to the short-term and the long-term prognosis. This study confirms the many inconsistencies concerning terminology, the need for antimicrobial treatment, duration of treatment, choice of drug and dosage.
The terminology that is used by the Dutch formularies was not consistent and was partly overlapping. A number of the terms used, such as chronic bronchitis, does not imply an infectious morbidity. The term "acute (tracheo)bronchitis" in microbiological literature refers to a diffuse inflammation of the trachea and larger bronchi, mostly seen in the winter months and is almost always of viral origin (2). Antibiotics are therefore not indicated in this disease. It is highly unlikely that this is the infection that is referred to in 79% of all Dutch formularies as "acute bronchitis"

and this term will probably refer to primary bacterial bronchitis in patients without underlying pulmonary disease. These infections are not very common however. Bacterial bronchitis is usually seen in patients with underlying pulmonary disease, most often COPD, characterised by expiratory obstruction with bronchospasm, excessive mucous production, bronchial inflammation and/or loss of elasticity in the small airways. Antibiotics are commonly used in the treatment of acute exacerbations of such chronic obstructive pulmonary disease. The term "exacerbation" is often related to "bacterial infection", although clear evidence for a bacteriological cause of the disease is lacking. In fact, the term "exacerbation" refers to a recent deterioration of the pulmonary complaints, without referring to the aetiology.
An objective diagnosis of bacterial bronchitis in patients with obstructive pulmonary disease is very difficult (3, 4). Fever or specific complaints are often lacking. The production of purulent sputum may be an indication of a bacterial infection, but in a number of cases no potentially pathogenic bacteria can be recovered from macroscopically purulent sputum (5). On the other hand the recovery of bacteria from sputum does not necessarily provide evidence for a bacterial aetiology, as 60% of all patients with COPD are colonised with bacteria. The remarks on the interpretation of the culture results of sputum in some formularies may therefore be justified.
There is still debate about the clinical and microbiological endpoints as efficacy parameters in the treatment of acute exacerbations of chronic bronchitis. A recent report by the FDA recommends two types of studies, one in which both clinical and microbiological endpoints are used and studies in which clinical criteria (return to baseline) are the only criteria (6).
The treatment of an exacerbation should be focussed primarily on reduction of bronchial inflammation and bronchospasm. This improves the mucociliary clearance and local defence factors, which will be sufficient for a number of patients to cure a potential bacterial infection. If signs of a bacterial infection (such as the production of purulent sputum) remain manifest after 2-3 days and no clinical improvement is observed, an antibiotic may be added to the therapeutic regimen after some days. Antibiotics

should be given earlier in patients with severe respiratory insufficiency and signs of lower respiratory tract infection.
In a surveillance study performed in 1989 by the Dutch Institute for Public Health and Environmental Protection, 5% of strains of *S.pneumoniae* were considered less susceptible to penicillin, whereas 6% of the tested strains of *H.influenzae* were resistant to amoxycillin through betalactamase production (7).
The amoxycillin dosages recommended in the Dutch antibiotic formularies were variable, although most formularies recommended a dose of 750 mg 3 times daily.
The recommended duration of treatment was more variable, although guidelines for the duration of treatment were only available in a small minority of the formularies. There is no consensus in the literature on this topic. Some studies recommend a short-term use (3-5 days) of antibiotics in exacerbation of chronic bronchitis, except in the case of severe bronchial disease (8, 9). More studies are needed before clear guidelines for the duration of treatment can be given.
The efficacy of antibiotics in exacerbation of chronic bronchitis is not very impressive in comparison with placebo, due to bias in patient-selection. Many studies have not clearly specified inclusion criteria. Only patients with a recent deterioriation of pulmonary complaints, purulent sputum and fever should be included in studies (4). It is very difficult to study sufficient numbers of patients to show differences between the efficacy of different dosages or different durations of treatment with the same antibiotic, especially if microbiological controls are also required (10).
It has been claimed that bacterial infections or colonisation of the respiratory tract are not causal factors in obstructive pulmonary disease nor do they have any effect on the natural course of COPD (11). The prophylactic use of antibiotics in patients with chronic bronchitis, bronchiectasis or emphysema, should therefore be abandoned and recommendations for the use of prophylactic antibiotics in antibiotic formularies should be omitted.

RECOMMENDATIONS

There appear to be few reasons to divide bacterial bronchitis into different subcategories, also because the antibiotic policy for both types of bronchitis is similar. We therefore suggest grouping lower respiratory tract infections into bacterial bronchitis and pneumonia. We strongly recommend a more uniform nomenclature. The large variations in the description of bronchial infections between the formularies lead to confusion for the user of these formularies and we suggest the term bacterial bronchitis.

The relevance of the underlying bronchopulmonary pathology for the diagnosis of bacterial bronchitis, the necessity of treatment with antibiotics and the interpretation of the potential effects of antibiotics must be considered in the formularies.

A number of antibiotics, such as amoxycillin, doxycycline and co-trimoxazole, are used in almost all Dutch antibiotic formularies. It is useful to present data on local resistance patterns in the formulary to document the antibiotic policy in the hospital in question. Regular epidemiologic surveillance of community-acquired respiratory tract isolates will support optimal empiric therapy for patients with bacterial bronchitis.

The diagnosis of bacterial bronchitis is not easy and the indication for starting antimicrobial treatment is not clearly described in any of the formularies.

The inclusion of relevant critical comments concerning the diagnosis and the indication for treatment with antibiotics in the formularies will probably result in a more rational use of these drugs and should stimulate discussion within the hospital. Such comments could be:

- Underlying pulmonary pathology should be considered in patients recurrently presenting with signs and symptoms of (possible) bacterial bronchitis and therapy should primarily be focussed on the treatment of the underlying pathology.
- Most episodes of acute (tracheo)bronchitis are of viral origin.
- The role of antibiotics in bacterial bronchitis in patients with COPD is unclear.
- Antibiotics are generally not indicated in patients with mucoid sputum.

- Repeated courses of antibiotics may lead to flora changes and the selection of resistant bacteria.
- There is no indication for antimicrobial prophylaxis in patients with COPD.

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CHAPTER V

ANTIBIOTIC POLICY IN DUTCH HOSPITALS
The treatment of pneumonia

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SUMMARY

The guidelines for the treatment of pneumonia as described in antibiotic formularies from Dutch hospitals are described. A total of 42 formularies, used in 92 Dutch hospitals were collected. Amoxycillin was the most frequently used agent in the treatment of community-acquired pneumonia and a wide variety of drugs was used for the treatment of nosocomial pneumonia, of these cefuroxime, alone or in combination with an amino-glycoside, was used most often. Benzylpenicillin was the most frequently used drug in community-acquired aspiration pneumonia; this drug, in combination with an aminoglycoside, was also the drug of choice in hospital-acquired aspiration pneumonia. A number of pneumonias with identified or presumed causative micro-organisms was also surveyed (the most usual drug of choice), such as pneumococci (benzylpenicillin), staphylococci (flucloxacillin), *H.influenzae* (amoxycillin), *Enterobacteriaceae* (cefuroxime), *Pneumocystis carinii* (co-trimoxazole), *Mycoplasma pneumoniae* (doxycycline and erythromycin) and *Legionella pneumophila* (e-rythromycin). Relatively wide variations in dosage-guidelines were observed for benzylpenicillin and amoxycillin. Only a limited number of formularies gave guidelines for the duration of treatment.

INTRODUCTION

Antibiotic policy is of great importance to reduce the development of (multiple)-resistant bacteria in hospitals and to achieve acceptable costs with adequate cover. Therefore, most Dutch hospitals (over 70%) have created antibiotic formularies with guidelines for the treatment of infections, specific for that hospital or for a group of collaborating hospitals.

Lower respiratory tract infections, such as bacterial bronchitis and pneumonia are very common in hospitals and are included in most antibiotic formularies. The recommendations for the treatment of pneumonia are reviewed in this article.

MATERIALS AND METHODS

By means of a written request to the members of the Dutch Association of Hospital Pharmacists (NVZA) we collected the antibiotic formularies from Dutch hospitals. The guidelines in these formularies were intended primarily for the treatment of hospitalised patients.
The following aspects of the antibiotic formularies were recorded:
- the classification of pneumonias (aetiology, causative micro-organisms).
- general recommendations concerning diagnosis and interventions in lower respiratory tract infections.
- guidelines concerning choice of antimicrobial drugs, dosage and duration of therapy for each individual infection.

RESULTS

A total of 43 antibiotic formularies was collected. One formulary was excluded, because it was too old (from 1983) to be a realistic guide for antimicrobial therapy.
Forty-two formularies from 92 Dutch hospitals (69% of all Dutch hospitals) were included in the study. The year of publication of these guidelines was as follows:

1985	1
1986	1
1987	3
1988	1
1989	3
1990	7
1991	9
1992	10
1993	7

Data on the classification of specific lower respiratory tract infections in the Dutch antibiotic formularies are presented in Table 1.

TABLE 1

FORMULARIES THAT GIVE GUIDELINES FOR THE TREATMENT OF CERTAIN LOWER RESPIRATORY TRACT INFECTIONS

Infection	Percentage of formularies
Community-acquired pneumonia (unknown pathogen)	93
Hospital-acquired pneumonia (unknown pathogen)	76
Aspiration pneumonia (community acquired) (unknown pathogen)	83
Aspiration pneumonia (hospital-acquired) (unknown pathogen)	76
Pneumonia with identified pathogen:	
- *Streptococcus pneumoniae*	90
- staphylococci	87
- *Haemophilus influenzae*	40
- *Moraxella catarrhalis*	26
- *Enterobacteriaceae*	76
- *Pseudomonas aeruginosa*	50
- Anaerobes	10
- Pneumocystis	67
- *Mycoplasma pneumoniae*	93
- *Chlamydia* spp	29
- *Legionella pneumophila*	88
- Psittacosis	50
- Ornithosis	36
- *Coxiella burnetii*	12
- *Mycobacterium tuberculosis*	60
- *Aspergillus* spp	36
- *Candida albicans*	29
Cystic fibrosis	19
Pulmonary abcess	57
Empyema	62

Community-acquired pneumonia

Community-acquired pneumonia with unknown pathogen was included in almost all antibiotic formularies. No data on the desired microbiological sampling (timing and number of sputum cultures) were presented in the formularies. Nineteen of the formularies (45%) stated that therapy should be based on the results of the Gram-stain of sputum, whereas one formulary stated that the diagnostic value of Gram-stain was very limited. Only seven formularies commented on the aetiology of community-acquired pneumonia. *Streptococcus pneumoniae* and *Haemophilus influenzae* were mentioned as possible causative micro-organisms in 7 formularies each, *Mycoplasma pneumoniae* was mentioned in three. Four formularies stated that also *Klebsiella pneumoniae* play a role in community-acquired pneumonia in alcoholics and 8 formularies specified that post-influenza pneumonia is usually caused by *Staphylococcus aureus*. Only one formulary presented detailed data on the susceptibility patterns in the hospital in question.

The drugs of choice for the treatment of community-acquired pneumonia are listed in Table 2.

TABLE 2

ANTIMICROBIAL AGENTS RECOMMENDED AS DRUGS OF CHOICE IN THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA WITH UNIDENTIFIED PATHOGEN IN 39 ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS

Drug	Percentage of formularies *
Amoxycillin	41
Ampicillin	5
Benzylpenicillin	15
Co-amoxiclav	8
Amoxycillin-gentamicin	3
Benzylpenicillin-flucloxacillin	3
Co-amoxiclav-erythromycin	3
Co-amoxiclav-tobramycin	3
Cefuroxime	13
Cefotaxime	3
Erythromycin	8
Co-trimoxazole	8

* the sum of the percentages is higher than 100, because some formularies recommended more than 1 drug as equal choices for this infection.

Amoxycillin is by far the most commonly used antibiotic, followed by benzylpenicillin and cefuroxime. Most formularies recommended an intravenous start of the treatment, with a switch to oral administration as soon as the condition of the patient had improved. The dose recommendations for all antibiotics were quite variable. The amoxycillin dose varied from 375 mg orally 3 times daily to 1-2 g iv 4 times daily. Thirty percent of all formularies recommended an amoxycillin dose of 1 g 4 times daily. The dose guidelines for benzylpenicillin varied from 0.25 million IU 4 times daily to 2 million IU every four hours. The most usual dose recommendations were 0.5 or 1 million IU 4 times daily, which were used in 48% of all formularies.

Ten formularies presented data on the duration of therapy. This ranged from 5-10 days in 8 formularies, whereas 2 others stated that therapy should be continued until 3 or 5 days after the patient became afebrile.

Hospital-acquired pneumonia

Hospital-acquired pneumonia with unidentified pathogen was included in 76% of the formularies. Only seven formularies commented on the microbiological aetiology of this form of pneumonia. All these formularies stated that Gram-negative bacilli were the most important causative micro-organisms in hospital-acquired pneumonia. Three of these formularies specified that the recovery of Gram-negative bacilli from sputum does not necessarily prove an infection.

A wide variety of treatment recommendations was given by the formularies and are summarized in Table 3. Although the wide variation is obvious from the Table, all treatment regimens provide at least some coverage against Gram-negative bacilli. All drugs were given by the intravenous route.

For those formularies that used intravenous cefuroxime as drug of choice, 38% recommended a dose of 750-1500 mg 3 times daily, 38% used a dose of 1500 mg 3 times daily, whereas 12% each used a dose of 750 mg 3 times daily, or a 1500 mg starting dose, followed by 750 mg 3 times daily. Almost all formularies recommended this treatment-regimen only as long as the culture results were unknown and to change to an appropriate regimen on the basis of these results. Only two formularies gave guidelines for the duration of treatment, this was 7 days in one formulary and 10 days in another.

TABLE 3

ANTIMICROBIAL AGENTS USED AS DRUGS OF CHOICE IN THE TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA WITH UNIDENTIFIED PATHOGEN IN 32 ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS

Drug	Percentage of formularies
Co-amoxiclav	6
Amoxycillin/gentamicin	9
Benzylpenicillin/gentamicin	3
Co-amoxiclav/gentamicin	6
Co-amoxiclav/tobramycin	6
Cefuroxime	22
Cefotaxime	3
Ceftizoxime	3
Cefazolin/tobramycin	3
Cefuroxime/gentamicin	19
Cefuroxime/netilmicin	3
Cefuroxime/pefloxacin	3
Cefamandole/gentamicin	3
Cefotaxime/erythromycin	3
Ceftriaxone/netilmicin	3
Co-trimoxazole	6

Aspiration pneumonia

Nine formularies made statements on the microbiological aetiology of aspiration pneumonia. Their conclusions were quite similar: Community-acquired aspiration pneumonia is caused primarily by anaerobic bacteria, susceptible to benzylpenicillin. In case of near-drowning, especially in polluted water, coverage against *Pseudomonas* spp. was considered important. Hospital-acquired aspiration pneumonia was caused both by anaerobes and by Gram-negative bacilli. Three of the formularies specified that in case of aspiration antibiotics should only be given in case of a documented pneumonia.

The treatment recommendations for community-acquired aspiration pneumonia and hospital-acquired pneumonia are summarized in Tables 4 and 5. The initial treatment was given by the intravenous route in all cases. Benzylpenicillin was the most widely used agent in cases of community-acquired aspiration pneumonia. Penicillin-based regimens were used in 87% of the Dutch antibiotic

TABLE 4

ANTIMICROBIAL AGENTS RECOMMENDED AS DRUGS OF CHOICE IN THE TREATMENT OF COMMUNITY-ACQUIRED ASPIRATION PNEUMONIA WITH UNIDENTIFIED PATHOGEN IN 35 ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS

Drug	Percentage of formularies
Benzylpenicillin	46
Amoxycillin	9
Ampicillin	3
Co-amoxiclav	17
Amoxycillin/gentamicin	3
Benzylpenicillin/clindamycin	3
Benzylpenicillin/netilmicin	3
Piperacillin	3
Cefuroxime	3
Cefuroxime/metronidazole	3
Clindamycin	9

formularies for this infection. All regimens provided coverage against anaerobes, with the possible exception of one formulary that recommended cefuroxime for this indication. Eight formularies presented guidelines for the duration of treatment for community-acquired aspiration pneumonia, ranging between seven and at least ten days.

A wider variety of treatment guidelines is observed in hospital-acquired aspiration pneumonia. All drugs were given intravenously. Benzylpenicillin plus an aminoglycoside or co-amoxiclav were the most often applied therapies. Penicillin-based regimens were used in 65% of all formularies, cephalosporin-based regimens in 21%, and 73% of all regimens included an aminoglycoside. Four formularies commented on the duration of treatment and this ranged between at least seven days and at least ten days.

TABLE 5

ANTIMICROBIAL AGENTS RECOMMENDED AS DRUGS OF CHOICE IN THE TREATMENT OF HOSPITAL-ACQUIRED ASPIRATION PNEUMONIA WITH UNIDENTIFIED PATHOGEN IN 32 ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS

Drug	Percentage of formularies
Co-amoxiclav	13
Piperacillin	3
Benzylpenicillin/gentamicin	22
Benzylpenicillin/tobramycin	6
Benzylpenicillin/netilmicin	3
Amoxycillin/gentamicin	3
Co-amoxiclav/gentamicin	9
Co-amoxiclav/tobramycin	6
Cefazolin/metronidazole	3
Cefuroxime/metronidazole	3
Cefuroxime/gentamicin	3
Cefuroxime/netilmicin	3
Cefuroxime/metronidazole/pefloxacin	3
Cefamandole/gentamicin	3
Cefotaxime/clindamycin	3
Clindamycin/gentamicin	3
Clindamycin/tobramycin	6
Clindamycin/netilmicin	3
culture results.....	3

Pneumococcal pneumonia

There was a consensus on the treatment of pneumococcal pneumonia. Benzylpenicillin was the drug of choice in all but one formulary, which recommended amoxycillin. Erythromycin was the most usual alternative drug in case of penicillin-allergy. The guidelines for the dosage of benzylpenicillin ranged between 1 and 12 million units per day. The majority of the formularies recommended a dosage of 2-4 million units benzylpenicillin per day. Eight formularies made statements on the duration of treatment. This ranged between five and ten days in six formularies and two formularies recommended continuation of therapy until 5 days after the patient became afebrile.

Staphylococcal pneumonia
Flucloxacillin was by far the most often recommended drug for the treatment of staphylococcal pneumonia. It was used alone in 33 formularies and in combination with gentamicin in three others. One formulary each recommended cloxacillin or cefuroxime. Ten formularies preferred benzylpenicillin to flucloxacillin in the case of a non-betalactamase producing *Staphylococcus aureus*. Vancomycin was not used for this indication. The dose recommendations for flucloxacillin ranged between 1 g 4 times daily and 2 g every four hours. Dosages of 1 g or 1-2 g every four hours were prescribed most often. Six formularies gave guidelines for the duration of treatment. This ranged between 7 and 21 days, with a mean of 14 days.

Pneumonia caused by *Haemophilus influenzae*
Amoxycillin was the drug of choice in this infection. It was used as drug of first choice in 15 out of 17 formularies, in doses ranging from 375 mg 3 times daily orally to 1 g 4 times daily intravenously, depending on the severity of the infection. Doxycycline was used by 5 formularies (several formularies presented more than one antimicrobial agent as equal alternatives) in a dose of 100 mg orally per day after a 200 mg loading dose. Co-trimoxazole and co-amoxiclav were used by 3 formularies each. The duration of treatment ranged between 7 and 14 days in 6 formularies.

Pneumonia caused by *Moraxella catarrhalis*
Pneumonia with *Moraxella catarrhalis* as causative organism was included in a relatively small number of antibiotic formularies. Of these, amoxycillin was used in 36%, benzylpenicillin in 9%, phenethicillin in 18%, co-amoxiclav in 18% and cefuroxime in 18%. Most formularies recommended both iv and oral administration, without giving clear guidelines when oral therapy was possible. A guideline for the duration of therapy was given in only 2 formularies. Both recommended a duration of 7 days.

Pneumonia caused by *Enterobacteriaceae*
Pneumonia caused by Gram-negative bacilli is an important

nosocomial infection. As stated above, three formularies specified that the recovery of Gram-negative bacilli from sputum is not an absolute evidence of a causal relationship between these bacteria and the symptoms of a respiratory tract infection.
The antibiotics used in the treatment of pneumonia caused by Gram-negative bacilli are presented in Table 6.

TABLE 6

ANTIMICROBIAL AGENTS RECOMMENDED AS DRUGS OF CHOICE IN THE TREATMENT OF PNEUMONIA CAUSED BY *ENTEROBACTERIACEAE* IN 32 ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS

Drug	Percentage of formularies
Co-amoxiclav	6
Amoxycillin/gentamicin	6
Co-amoxiclav/gentamicin	6
Co-amoxiclav/tobramycin	3
Cefuroxime	19
Cefotaxime	13
Cefazolin/gentamicin	6
Cefazolin/tobramycin	3
Cefuroxime/gentamicin	16
Cefuroxime/netilmicin	3
Cefamandole/gentamicin	3
Cefamandole/netilmicin	3
Ceftriaxone/netilmicin	3
Co-trimoxazole	9

Twenty-one percent of the formularies recommended a penicillin-containing regimen, whereas 69% recommended a cephalosporin-based therapy. Aminoglycosides were used in 52% of all formularies. There was no clear relationship between the year of publication of the formulary and the preference for penicillins or cephalosporins. The dose of cefotaxime advised ranged between 3 and 6 g per day in 3-6 doses. Guidelines for the duration of therapy were given in only 3 formularies, ranging from 10 to 21 days.
One formulary presented data on the susceptibility of *E.coli, Klebsiella* and *Enterobacter cloacae* to first and second generation cephalosporins in that hospital. The susceptibility of *E.coli* was

85% to first generation cephalosporins and 100% to cefuroxime. The susceptibility of *Klebsiella* spp. was similar: 94% to the first generation and 96% to cefuroxime. Forty percent of all strains of *Enterobacter cloacae* were susceptible to first generation cephalosporins, whereas the susceptibility to cefuroxime was 70%. On the basis of these findings this hospital used a combination of cefuroxime and gentamicin for this indication.

Pneumonia caused by *Pseudomonas aeruginosa*

The guidelines for the treatment of this form of pneumonia are presented in Table 7.

TABLE 7

ANTIMICROBIAL AGENTS RECOMMENDED AS DRUGS OF CHOICE IN THE TREATMENT OF PNEUMONIA CAUSED BY *PSEUDOMONAS AERUGINOSA* IN 21 ANTIBIOTIC FORMULARIES FROM DUTCH HOSPITALS

Drug	Percentage of formularies
Amoxycillin/tobramycin	5
Piperacillin	5
Piperacillin/gentamicin	14
Piperacillin/tobramycin	38
Piperacillin/netilmicin	5
Ticarcillin/gentamicin	10
Ticarcillin/tobramycin	5
Cefsulodin	5
Ceftazidime/tobramycin	5
Ceftazidime/netilmicin	5
Ciprofloxacin/tobramycin	5

The roles of cephalosporins and fluoroquinolones in this infection are still limited. Cephalosporins were used in only 15% of all formularies and ciprofloxacin in only one. This drug was recommended as drug of second choice in 2 formularies (10%). The vast majority (92%) of all formularies used an aminoglycoside-containing regimen for this indication.

Pneumocystis carinii pneumonia

There was a consensus on the drug of choice for the treatment of pneumonia caused by *Pneumocystis carinii*. All 28 formularies that included this infection, recommended co-trimoxazole as the drug of choice. Fifteen of these (54%) used a dosage of 1920 mg (1600 mg sulfamethoxazole plus 320 mg trimethoprim) 3 times daily orally or intravenously. A variety of other dosages was used in the other formularies, ranging from 480 mg 5 times daily to 2280 mg twice daily. Pentamidine was used as an alternative drug in 5 formularies.

Atypical pneumonia

Atypical pneumonia, caused by *Mycoplasma pneumoniae, Chlamydia pneumoniae, C.psittaci* or *Legionella pneumophila*, was included in most formularies.

Doxycycline was the drug of choice in 77% of the formularies for mycoplasmal pneumonia and erythromycin in 69% (several formularies considered both drugs as equal). Roxithromycin was preferred to erythromycin in one formulary. One formulary used erythromycin when intravenous administration was considered necessary and roxithromycin if oral dosage was possible. The daily dose for erythromycin was 2 g in 25 formularies and 4 g in two formularies. The daily dose for doxycycline was 100 mg (after a 200 mg loading dose) in 23 formularies and 200 mg in nine formularies. Sixteen formularies included data on duration of treatment and nine of them recommended a duration of two weeks, whereas the others varied from 7 days until at least 21 days.

Erythromycin was the drug of choice in case of pneumonia caused by *Legionella pneumophila* in all but one formularies. In severe cases, rifampicin was added to the regimen. Pefloxacin was the drug of choice in one formulary. The dose of erythromycin was 1 g 4 times daily intravenously in 32 out of 36 formularies that used this drug. In the other formularies, a daily dose of 2-4 g was used. Seventeen formularies gave guidelines for the duration of treatment. Ten of these recommended a duration of treatment of 21 days, the guidelines in the other formularies ranged from 7 to 28 days.

Psittacosis and ornithosis were treated with doxycycline in all but one cases: one formulary preferred tetracycline. The daily dose of doxycycline was 100 mg (after a starting dose of 200 mg) in 83% of cases and 200 mg in 17%. Guidelines on duration of therapy were given in 11 formularies. These ranged from 7 to 21 days.

Pneumonia caused by yeasts or fungi

Invasive aspergillosis was included in a limited number of formularies. In all cases amphotericin B was considered to be the drug of choice. In 64% of these the drug was combined with flucytosine. Itraconazole was used as alternative drug in 4 formularies. Dose recommendations and guidelines for the duration of treatment were given in a limited number of formularies. Most formularies recommended consultation with a medical microbiologist in case of this infection. Invasive candidiasis was also treated with a combination of amphotericin B and flucytosine. One formulary preferred ketoconazole and three used this as an alternative drug to the amphotericin B-flucytosine combination. Guidelines on duration of therapy were lacking.

Pulmonary abcess

Most formularies considered drainage of the abcess as the primary treatment. Of the 24 formularies that mentioned this disease, eight (33%) recommended treatment only on culture results. Of the remaining 16 formularies, 5 (31%) used benzylpenicillin for this indication. The dosages of benzylpenicillin were higher than those used for (proven or suspected) pneumococcal pneumonia and ranged between 6 and 24 million units per day. A wide variety of other drugs was used in one formulary each.

DISCUSSION

Successful treatment of pneumonia depends on a variety of patient-related factors, such as the status of host-defence, underlying disease and age, on the type and severity of the infection, the pathogenicity and susceptibility of the offending pathogen and the choice of antimicrobial therapy (1).

Most Dutch hospitals have created guidelines for the treatment of infections. None of the antibiotic formularies that we studied gave clear references on which the recommendations for the treatment of pneumonia were based. Only 2 of the formularies explained their choice of antimicrobials by means of a discussion section of which one also presented susceptibility data, specific for that hospital. In the ideal situation the choice of antimicrobial drugs in the hospital should be based on well defined susceptibility data in the hospital in question. In an earlier survey we have shown that these data, specified by source, ward and the incidence of various pathogens in a specific infection were readily available from only 5 out of 78 Dutch hospitals (2). As these data are lacking it is not possible to comment on all the choices that are made by the Dutch hospitals.

The most important causative micro-organisms involved in community-acquired pneumonia are *S.pneumoniae, H.influenzae M.pneumoniae* and *M.catarrhalis. S.pneumoniae* is most frequently isolated (3, 4). Bacterial pneumonia, especially pneumococcal pneumonia usually presents the typical signs and symptoms of acute onset, high fever, pleuritic pain, productive cough, marked leukocytosis and lobar infiltrations on the chest X-ray. The so-called "atypical" pneumonia will present less acutely with a prodromal phase and with milder symptoms. In addition to interstitial infiltrates and nonproductive cough, the fever is limited and there is usually only moderate leukocytosis. In many cases the signs and symptoms are frequently not as characteristic as described previously (5). Mycoplasma pneumonia is seen most frequently in children over the age of six and in young adults (6). The susceptibility of *S.pneumoniae* and *H.influenzae* to amoxycillin in the Netherlands is still very good, with >99% of *S.pneumoniae* and >95% of *H.influenzae* being susceptible. Sixty-five percent the isolates of *M.catarrhalis* was resistant to amoxy-cillin (7). Although amoxycillin is generally considered to be inactive against *Chlamydia pneumoniae* and *M.pneumoniae*, recent studies suggest that both amoxycillin and co-amoxiclav possess in-vivo activity against *Chlamydia trachomatis* (8).

The choice of amoxycillin for community-acquired pneumonia, also considering the very wide clinical experience with the drug, appears to be a rational one, although all the antibiotics included in Table 3 possess activity against the great majority of causative micro-organisms. A disadvantage of erythromycin is the limited activity against *H.influenzae*. Its intravenous form is very costly and drug administration is not always problem free. *Legionella pneumophila* is rarely observed in community-acquired pneumonia, except in patients who have recently been abroad. As the number of double-blind comparative studies between two or more antibiotics in community-acquired pneumonia is very small, no clear statements can be made concerning the choice, dosage and duration of treatment. The wide variation in recommendations found in the formularies therefore reflects the lack of well-designed clinical studies.

The predominant micro-organisms involved in nosocomial pneumonia are Gram-negative bacilli (such as *E.coli, K.pneumoniae, E.cloacae* and *P.aeruginosa*), followed by *S.pneumoniae* and *S.aureus*, but a wide variety of other micro-organisms can be seen (1). Most Dutch hospitals use second generation cephalosporins alone or in combination with an aminoglycoside. In a survey performed by the Dutch National Institute of Public Health and Environmental Protection (RIVM) in 1988, the percentages of resistance of *E.coli* to first, second and third generation cephalosporins were 8%, 2% and 1%, respectively, whereas the percentages for *Klebsiella* spp. were 9%, 8% and 1%, respectively. The situation was quite different for *Enterobacter* spp., where 74%, 16% and 3% were resistant. The activity of gentamicin against these bacteria was excellent, with only 4% of Enterobacter being resistant to the drug (9). As recent nation-wide and published local data on the susceptibility of *Enterobacteriaceae* are lacking, it is impossible to comment on the recommendations made in the formularies.

Some formularies specify that the recovery of Gram-negative bacilli from sputum is not absolute evidence for the presence of an infection caused by these bacteria. The oropharynx of patients who stay in the hospital for longer than a few days is often colonized by Gram-negative bacilli. The presence of Gram-negative bacilli must therefore always be considered in a clinical context (10).

The choice of benzylpenicillin for community-acquired aspiration pneumonia is similar to that Reese and Douglas from the USA

(11). These authors however advise a cephalosporin plus an aminoglycoside in case of a hospital-acquired aspiration pneumonia. This regimen is used in only one of the Dutch antibiotic formularies. The Belgian guidelines (1) recommend imipenem or ticarcillin-clavulanic acid for this infection. None of the Dutch antibiotic formularies used this approach.

There is a consensus on the choice of an agent for pneumococcal pneumonia, although the guidelines for dosages of benzylpenicillin were highly variable. Studies that specifically investigated the dose and duration of therapy with benzylpenicillin are lacking. Aoun and Klastersky (1) recommend a dose of 8 million units daily, but it is not clear what is the basis of their guidelines, whereas Reese and Douglas (11) recommend a dose of 1.2 to 2.4 million units per day.

Staphylococcal pneumonia is a very serious disease, with a high rate of mortality. Staphylococcal pneumonia is seen frequently as a secondary bacterial infection after an initial viral infection of the respiratory tract (post-influenza pneumonia). Aggressive antibiotic treatment is necessary. It is not clear whether combination treatment with an aminoglycoside yields better results than monotherapy with a betalactam antibiotic with sufficient activity against staphylococci.

The vast majority of *S.aureus* isolates are susceptible to flucloxacillin and the choice of this drug in Dutch hospitals is therefore a logical one. Some formularies recommend the use of benzylpenicillin in case of a documented infection with a non-betalactamase producing strain. The incidence of methicillin-resistant *S.aureus* (MRSA) is very low in the Netherlands, so there is no reason to recommend the routine use of vancomycin or teicoplanin for staphylococcal pneumonia. Again the wide variety in dose recommendations reflects the lack of controlled studies in this rare infection.

Most formularies made no clear distinction between infections for which it has been proven that *H.influenzae* or *M.catarrhalis* are the causative bacteria, with a well defined susceptibility pattern and infections probably caused by these bacteria, without any data on susceptibility. Pneumonia primarily caused by one of these bacteria is rare, however. The choice of amoxycillin is correct if

susceptibility to this antibiotic has been demonstrated, but it is not a correct initial treatment for infections probably caused by *M.catarrhalis*, without knowledge of the susceptibility to the drug, as about 65% of all strains were resistant to amoxycillin (7).
Both second and third generation cephalosporins, with or without an aminoglycoside were recommended for the treatment of pneumonia caused by Gram-negative bacilli in the Dutch formularies. In Belgium, third generation cephalosporins or aztreonam were recommended for this indication (1). A greater use of broad-spectrum antimicrobial agents, such as the third generation cephalosporins, aminoglycosides, fluoroquinolones, imipenem and aztreonam in Belgium has been described in comparison with the Netherlands (12). As there are large differences in susceptibility to antibiotics between different countries, the results of comparative studies from the United States, Japan or southern Europe are not necessarily also valid for the Dutch situation. The same is true for recommendation from other countries. This is also recognised by Reese and Douglas from the USA, who recommend a cephalosporin plus an aminoglycoside for this indication, but leave the choice of the type of cephalosporin to the individual hospital, to be based on local susceptibility data (11).
The low use of ceftazidime for the treatment of pseudomonal pneumonia is surprising, considering the relatively large number of studies with this agent. Most Dutch formularies prefer a combination of piperacillin and an aminoglycoside, as do Reese and Douglas (11).
Fluoroquinolones have not yet become an important group of drugs for this indication, despite their good in-vitro activity and good penetration of lung tissue.
The guidelines for the treatment of infections in the formularies caused by *Pneumocystis carinii* are well in accordance with Dutch guidelines (13) and international recommendations for the treatment of these infections (14) : 90-120 mg/kg oral or intravenous co-trimoxazole daily.
Cost should play an important role in the selection of antimicrobial agents in hospital. The realistic acquisition costs for a number of antimicrobial agents, valid for the average Dutch hospital are shown in Table 8.

TABLE 8

COST OF ANTIMICROBIAL AGENTS (mean realistic cost, including VAT, for an average Dutch hospital)

Drug	Daily dose (g)	Daily cost (NLG)
Benzylpenicillin	4 million IU	7
Amoxycillin	4 (iv)	15
	2 (oral)	3
Ampicillin	4 (iv)	12
Co-amoxiclav	3 6 (iv)	30
Flucloxacillin	6 (iv)	38
	4 (oral)	8
Cefazolin	4 (iv)	18
Cefuroxime	4 5 (iv)	72
Cefuroxime axetil	1 0 (oral)	10
Cefotaxime	3 (iv)	66
Cefpodoxime	0 4 (oral)	10
Ceftazidime	3 (iv)	115
Piperacillin	12 (iv)	110
Metronidazole	1 5 (iv)	12
	1 5 (oral)	2
Gentamicin	0 24 (iv)	10
Erythromycin	4 (iv)	120
Roxithromycin	0 3 (oral)	6
Ofloxacin	0 6 (iv)	120
	0 6 (oral)	8

These prices are sometimes quite different from the official wholesale prices, especially in case of cefazolin and gentamicin. The acquisition costs of ampicillin injections are lower than those of amoxycillin, although both penicillins are relatively inexpensive. The clinical efficacy and tolerance of both drugs after parenteral administration is quite similar. The cost of co-amoxiclav is about double that of amoxycillin-injections. In the Dutch situation, there is no great difference in cost between cefuroxime and cefotaxime. The latter agent is in many hospitals even less expensive, when dosages of 1.5 g cefuroxime 3 times daily and cefotaxime 1 g 3 times daily are compared.
For all antimicrobial drugs the oral forms are much cheaper than the parenteral formulations. This is especially true for the fluoroquinolones, the macrolides and also for the cephalosporins.

It is not always necessary to start with intravenous antibiotics. This depends mainly on the clinical condition of the patient, although there are no generally accepted guidelines for which patients should receive parenteral antibiotics. Intravenous administration is considered necessary in case of dehydration, disturbed bowel motility or circulatory instability. Almost all Dutch antibiotic formularies recommended initial treatment with parenteral antibiotics and only a limited number of formularies contained statements about a switch to oral antibiotics, when the condition of the patient had improved. Although the potential savings of an early switch from parenteral to oral cephalosporins are enormous (15), virtually no literature is available on this subject.
Studies are also lacking on the dosage and duration of antibiotic treatment for the treatment of the different forms of pneumonia. Most Dutch formularies contained no statements on the important subject of duration of therapy. It is common practice in Dutch hospitals to continue antibiotic treatment until 48 h after the patient becomes afebrile (personal communications). This is however not clearly stated in the formularies.

CONCLUSIONS

The classification of pneumonia in the Dutch antibiotic formularies is quite diverse. Guidelines for the treatment of pneumonia with unknown pathogen are probably of greater importance than those with an identified pathogen with a well defined susceptibility pattern. The therapy for the latter group of pneumonias will be based also on culture results. A more uniform approach to the classification of pneumonias is recommendable.
The wide variety in dose recommendations and the very limited information on the duration of antimicrobial therapy reflects the absence of controlled clinical studies investigating the importance of dosage, dosage frequency, route of administration and duration of treatment. This is mainly caused by the fact that studies of this kind are usually not sponsored by the pharmaceutical industry.
As available data on susceptibility patterns of bacteria are lacking, it is not possible to comment on the choice of antimicrobial agents

in the Dutch formularies. It is generally agreed that these data must form the basis of the antimicrobial policy in the hospital. These susceptibility data should therefore be readily available in the preparation of antimicrobial policy and they may also provide insight whether there is any scientific basis for the wide variety of treatment recommendations which have been observed in this study.

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CHAPTER VI

ANTIBIOTIC POLICY IN DUTCH HOSPITALS
The treatment of sepsis

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SUMMARY

The guidelines for the treatment of sepsis as described in antibiotic formularies from Dutch hospitals are reviewed. A total of 39 formularies, used in 88 Dutch hospitals were collected and analysed. The guidelines for the treatment of sepsis of unknown aetiology or sepsis with a focus in the urinary tract, respiratory tract or intra-abdominal sepsis are discussed. Betalactam antibiotics (especially amoxycillin and cefuroxime), almost always in combination with an aminoglycoside, were the preferred agents for the treatment of sepsis with an unidentified pathogen. Aminoglycosides were included in most schedules for all presentations of sepsis. Substantial differences were observed in the choice and dosage of antimicrobial agents for the treatment of sepsis. Due to the lack of local data on the susceptibility of blood isolates from Dutch hospitals, the guidelines are not properly interpretable, although data from a Dutch surveillance study suggested that the resistance of Enterobacteriaceae to cefuroxime and co-trimoxazole was quite variable.

INTRODUCTION

Bacteraemia refers to the detection of bacteria in the blood. It is therefore a microbiological laboratory finding which gives little information about the clinical situation of the patient. While bacteraemia can be transient, self-limiting and of little clinical significance, sepsis constitutes a vital medical emergency, that needs a systematic diagnostic approach and aggressive therapy aimed at terminating bloodstream invasion by the infecting microorganism and correction of the pathophysiological sequelae (1). Adequate guidelines for the treatment of sepsis are therefore of great importance (2).

Most Dutch hospitals have created antibiotic formularies with written guidelines for antibiotic policy, specific for that hospital or for a group of collaborating hospitals (3). In this article the guidelines for the treatment of sepsis in Dutch antibiotic formularies are analysed and discussed.

MATERIALS AND METHODS

By means of a written request to the members of the Dutch Association of Hospital Pharmacists (NVZA) we collected the antibiotic formularies from Dutch hospitals. Only those formularies were included in the study in which guidelines for the treatment of sepsis were given. This analysis focussed on guidelines for the treatment of sepsis with unidentified pathogen.

The following aspects were recorded:

- the definition of sepsis.
- general recommendations concerning diagnosis and interventions in sepsis.
- guidelines concerning choice of antimicrobial drugs, dosage and duration of therapy for the treatment of sepsis with unknown aetiology or with a known focus.

Guidelines for the treatment of neutropenic patients were not included in the study.

RESULTS

A total of 42 antibiotic formularies were collected. Three formularies contained no guidelines for the treatment of sepsis and were therefore excluded.

Thirty-nine formularies used in 88 Dutch hospitals were included in the study. The years of publication of these guidelines were as follows:

	N
1983	1
1985	1
1986	1
1987	3
1988	1
1989	3
1990	7
1991	8
1992	9
1993	5

The percentage of formularies that contained guidelines for various subtypes of sepsis with unknown pathogen is summarized in Table 1.

TABLE 1

GUIDELINES FOR THE TREATMENT OF SEPSIS WITH UNKNOWN PATHOGEN IN DUTCH ANTIBIOTIC FORMULARIES

Type of sepsis	No. of formularies (%) in which it is included
unknown	31 (79%)
Urinary tract	24 (62%)
Respiratory tract	21 (54%)
Upper gastrointestinal tract	18 (46%)
Lower gastrointestinal tract	26 (67%)
Biliary tract	21 (54%)
Skin	12 (31%)
Female genital tract	14 (36%)
Intravenous line	7 (18%)
Osteomyelitis	4 (10%)

The most commonly included presentations of sepsis were sepsis of unknown aetiology and source, which was included in 31 formularies (79%) and sepsis with a known or suspected focus in the lower gastrointestinal tract, included in 26 formularies (67%).
A definition of sepsis was given in one formulary only. One out of the three formularies that did not provide guidelines for the treatment of sepsis was a "preliminary" version. Although it did not yet give recommendations for the treatment of sepsis, it contained detailed data on the culture results in the hospital in question. None of the other formularies provided any data on the culture results or the susceptibility patterns of the hospital.
Eleven formularies presented guidelines for the microbiological sampling of patients with clinical signs and symptoms of sepsis. A minimum of 3 blood cultures was recommended by eight of these formularies.
The guidelines for the treatment of *sepsis of unknown aetiology* are presented in Table 2.

TABLE 2

DRUGS OF CHOICE FOR THE TREATMENT OF SEPSIS OF UNKNOWN AETIOLOGY (included in 31 formularies)

	As such	Combination amino	Combination metro	Combination amino and metro
Amoxycillin		5		1
Ampicillin		4		
Co-amoxiclav		4		
Piperacillin		1		
Cefazolin		1		
Cefalothin		1		
Cefuroxime	2	9		1
Cefamandole	1	1		
Cefotaxime	1	1		
Ceftriaxone		1		
Cefuroxime/pefloxacin			1	

Amino = aminoglycoside
Metro = metronidazole
Some formularies present more than one option

Aminoglycosides were included in the therapeutic regimen in 28 of 31 formularies (90%) that provided guidelines for this form of sepsis. Of these, gentamicin was the aminoglycoside of choice in 20 formularies, tobramycin in five and netilmicin in three. Amikacin was not used as initial aminoglycoside in any of the hospitals. All regimens contained a penicillin or a cephalosporin. Cefuroxime and amoxycillin or ampicillin were the most popular betalactam antibiotics. The dose of cefuroxime was 1500 mg 3 times daily in 10 of 12 formularies, whereas the dose of amoxycillin and ampicillin ranged between 1 g 4 times daily (the most commonly used dose) and 2 g 6 times daily. All antibiotics were given by the intravenous route.

The guidelines for the treatment of *urosepsis* are summarized in Table 3. Three formularies commented on the microbiological aetiology of urosepsis. All these stated that the most likely pathogens involved in urosepsis were *Enterobacteriaceae*, enterococci and (less frequently) *P.aeruginosa*.

TABLE 3

DRUGS OF CHOICE FOR THE TREATMENT OF UROSEPSIS
(included in 24 formularies)

	As such	Combination with aminoglycoside
Amoxycillin		4
Ampicillin		1
Co-amoxiclav	1	1
Cefazolin	1	2
Cefuroxime	5	6
Cefotaxime	1	
Cotrimoxazole	1	
Pefloxacin	1	
Aminoglycoside	2	-

Some formularies present more than one option

Aminoglycosides were added to betalactam antibiotic less frequently than was the case for sepsis of unknown aetiology. In four formularies, a regimen without a betalactam antibiotic was recommended. One formulary used a fluoroquinolone (pefloxacin) for this indication. Another formulary initially used cefotaxime, with a switch to oral ofloxacin after about 3 days. All other formularies recommended antibiotics to be given by the intravenous route for the total duration of therapy.

A wide variety of treatment recommendations was observed for sepsis originating from the female genital tract. Of 14 formularies, two recommended monotherapy with co-amoxiclav, three used a combination of either co-amoxiclav, cefuroxime or piperacillin with an aminoglycoside. Three formularies used an aminoglycoside with metronidazole and three other formularies recommended these drugs in combination with a betalactam antibiotic. The remaining formularies preferred a combination of a betalactam antibiotic and metronidazole.

The recommendations for the treatment of *sepsis probably originating from the respiratory tract* are presented in Table 4.

TABLE 4

DRUGS OF CHOICE FOR THE TREATMENT OF SEPSIS, WITH A SUSPECTED FOCUS IN THE RESPIRATORY TRACT
(included in 21 formularies)

	As such	Combination with aminoglycoside
Amoxycillin	1	4
Ampicillin	1	
Benzylpenicillin	4	2
Co-amoxiclav	1	3
Amoxycillin/erythromycin	1	
Flucloxacillin	1	
Cefuroxime	1	7
Cefuroxime/erythromycin	1	
Cefuroxime/pefloxacin	1	

Some formularies present more than one option

One formulary specified that coverage against Gram-positive cocci and *H.influenzae* was important, whereas two other formularies stated that the most likely pathogen was *S.pneumoniae*, either alone or in combination with other bacteria, such as *P.aeruginosa* or enterococci. A betalactam antibiotic was included in all regimens. Of the cephalosporins, only cefuroxime was used in the formularies, whereas a variety of penicillins were recommended. Aminoglycosides were added to the regimens in 16 of 18 formularies. Two formularies stated that the use of aminoglycosides was necessary in severe cases of sepsis. Erythromycin was added to amoxycillin or cefuroxime in two formularies, probably for coverage of atypical pathogens, such as *Chlamydia pneumoniae, Mycoplasma pneumoniae* or *Legionella pneumophila.*

The guidelines for the treatment of *sepsis originating from the upper or lower digestive tract* are presented in Table 5. The three formularies that provided information on the most likely pathogens all stated that coverage of Gram-negative bacilli, including *Salmonella* spp., enterococci and anaerobes was important.

TABLE 5

DRUGS OF CHOICE FOR THE TREATMENT OF INTRA-ABDOMINAL SEPSIS, WITH A SUSPECTED FOCUS IN THE UPPER OR LOWER DIGESTIVE TRACT
(included in 26 formularies)

UPPER DIGESTIVE TRACT

	As such	Combination amino	Combination metro	Combination amino and metro
Amoxycillin		3		2
Ampicillin	1			
Benzylpenicillin				1
Co-amoxiclav	1	1		
Piperacillin		1		
Cefuroxime	1	1	1	2
Co-trimoxazole	1			
Clindamycin		1		
Pefloxacin				1

LOWER DIGESTIVE TRACT

	As such	Combination amino	Combination metro	Combination amino and metro
Amoxycillin		1		3
Co-amoxiclav	2	1		1
Piperacillin		1		
Cefuroxime			3	3
Cefotaxime			1	
Clindamycin		1		
Pefloxacin				1
---				9

A wide variety of treatment recommendations were given in the formularies for sepsis originating from the upper digestive tract. No more than 3 formularies gave similar recommendations, but even for these the dosage guidelines differed. Aminoglycosides were used in 13 of 18 formularies (72%) and metronidazole or clindamycin were used in 8 of 18 (44%).

A coverage of anaerobic bacteria was recommended by more formularies for the treatment of sepsis originating from the lower digestive tract: Metronidazole or clindamycin were used by 81%

of the formularies and an aminoglycoside was also recommended by 81%. A combination of an aminoglycoside (mostly gentamicin) and metronidazole (1500 mg daily in 1-3 doses in all cases) without a betalactam antibiotic was used in 33% of the formularies.

Twenty-one formularies presented recommendations for *biliary sepsis*. A similar pattern of causative micro-organisms was described for biliary sepsis as was that for sepsis originating from the digestive tract in three formularies. Monotherapy with betalactam antibiotics (1 x piperacillin and 1 x cefazolin) was given in only two formularies. A combination of a betalactam antibiotic and an aminoglycoside was used in 12 formularies, of which five used a combination of amoxycillin and gentamicin. Co-amoxiclav and an aminoglycoside were recommended in three formularies. The other formularies recommended a combination of a betalactam antibiotic, an aminoglycoside and metronidazole.

Sepsis originating from the skin was treated with a penicillin in 10 of 12 formularies, flucloxacillin being used in all but two cases. The dose of flucloxacillin ranged between 4 and 12 g per day, a dose of 1-2 g 6 times daily was used most frequently. In two formularies flucloxacillin was used in combination with amoxycillin or benzylpenicillin and in two other formularies the drug was combined with gentamicin. Staphylococci were mentioned as most likely pathogens by three formularies.

Only seven formularies included guidelines for the treatment of *sepsis originating from an intravenous or arterial line*. Flucloxacillin was used most often (four times), followed by cefuroxime (1x), vancomycin (1x) and vancomycin + gentamicin (1x).

The intravenous route was recommended by the formularies for all forms of sepsis. The antibiotics were usually given by intermittent infusion; two formularies recommended continuous infusion of betalactam antibiotics as an alternative to intermittent infusion. One of these used similar dosages for continuous and intermittent infusion, whereas the other formulary used lower dosages with continuous infusion.

Only nine formularies (23%) gave recommendations for the duration of therapy. This ranged from 10-14 days in eight formularies;

continuation of therapy for 3-5 days after clinical improvement was advised in one formulary.

DISCUSSION

Two groups of formularies can be distinguished. In one group, representing approximately 2/3 of all formularies, guidelines for the treatment of sepsis are given depending of the focus of an infection, as is described in Tables 1-5. Besides this, guidelines are also given for the treatment of sepsis with an established causative micro-organism. The other formularies, about 1/3 of all, only present data on those forms of sepsis in which the causative micro-organism has been demonstrated or suspected. Guidelines for the treatment of sepsis caused by *S.aureus* are present in 33 formularies, enterococci in 25, *Enterobacteriaceae* in 23 and *E.coli* in 21.
The antibiotic formularies from Dutch hospitals present guidelines for the antimicrobial treatment of the infectious process. No recommendations for the supportive therapy are given in any formulary.

Microbiological sampling
Those formularies that contain statements on the micro-biological sampling of patients with sepsis all recommend sampling of at least 3 blood cultures. This is well in accordance with the recommendations given in the literature. Washington et al. and Weinstein et al. clearly showed the value of obtaining more than one single blood culture (4, 5). Detection of more than 99% of the positive blood cultures required two or three blood cultures mainly because the yield largely depends on the volume of blood cultured.

Causative micro-organisms
One antibiotic formulary in this study contained data on the prevalence of bacteria in positive blood cultures. In that hospital 67% of all positive blood cultures yielded Gram-positive bacteria and 29% Gram-negative bacteria. The most frequently isolated bacteria were *S.epidermidis* (25%), *S.aureus* (13%), streptococci (8%) and *E.coli* (16%). *P.aeruginosa* was found in only 1% of all 330 isolates. In

an earlier study from Germany, performed in 1982, about 50% of all causative bacteria were Gram-positive and the other half were Gram-negative (6). *E.coli* was by far the most important Gram-negative isolate, representing over 50% of all Gram-negative bacteria. *P.aeruginosa* was found in about 5% of all Gram-negative isolates. For the empiric therapy, a distinction must also be made between community-acquired sepsis and hospital-acquired sepsis. Gram-negative bacteria (including *P.aeruginosa*) and fungi are isolated more often in hospital-acquired sepsis than in community-acquired sepsis (7).

Gram-negative, Gram-positive and fungal infections may all have similar clinical presentations. If there is no clear focus of infection and the patient has no obvious underlying disease, the most probable micro-organisms are Gram-positive cocci and Gram-negative bacilli (7). An analysis of 500 episodes of bacteraemia in adults showed that two-thirds of the isolates were hospital-acquired (4). In a more recent study from the United Kingdom, 60% were hospital-acquired (8). Pneumococci were community-acquired in 81%. *Enterobacteriaceae* were usually hospital-acquired, except *E.coli*, which were community-acquired in more than 40%.

Most Dutch formularies made no distinction between hospital- and community acquired sepsis. According to the study of Weinstein et al. (4) pneumococci, *S.aureus* and *P.aeruginosa* were the species most frequently isolated in case the sepsis originated from the respiratory tract, followed by streptococci and *Enterobacteriaceae*, which were isolated with equal frequency. The seasonal variations of pneumococcal isolation, peaking in late winter was striking (4). In the study of Eykin (8) 22% of the community-acquired septicaemias were caused by *S.pneumoniae*, mostly (80%) originated from the respiratory tract.

A variety of bacteria is found in intra-abdominal sepsis. This form of sepsis is almost always polymicrobial. The most frequent isolates are *E.coli* (57%), *Bacteroides* spp. (43%), streptococci (25%), enterococci (23%), *Clostridium* spp. (18%), *Klebsiella* (15%) and *Pseudomonas* spp. (15%). Surgery plays an important role in the treatment (9).

Availability of susceptibility data in Dutch hospitals

In an earlier study (3), we have shown that the situation regarding the availability of susceptibility data from Dutch hospitals is far from ideal. Therapy for the treatment of sepsis of unknown aetiology should be based primarily on the prevalance of bacteria causing sepsis and on the relative susceptibility of these bacteria to different antimicrobial agents. An epidemiological surveillance of the antibiotic resistance in the hospital is very important for assessment of a blind antibiotic policy (10) and the Dutch situation is therefore open to improvement.

Recently, the data from a large-scale surveillance study performed by De Neeling et al. in the Netherlands became available, with susceptibility data from 7 microbiological laboratories (representing approximately 25% of the Dutch population) in the period 1990-1992 (11). Over 377,000 isolates were included in this study. Of these, 51% were clinical isolates, 27% from out-patient clinics, 8% from nursing homes and 14% from general practice.

Amoxycillin had only modest activity against *Enterobacteriaceae,* but no significant resistance of pneumococci to this agent has been shown. Co-amoxiclav showed excellent in-vitro activity against the tested respiratory tract pathogens, but its activity against *Enterobacteriaceae* was limited, especially at the "low" breakpoint. Important differences were observed in susceptibility of *Enterobacteriaceae* to cephalosporins of the first (cefazolin), second (cefuroxime) and third generation (cefotaxime and ceftazidime). This was especially the case for the "low" breakpoints of 4 mg/l. If the "high" breakpoint of 16 mg/l is maintained, cefuroxime showed good in-vitro activity. All cephalosporins showed excellent activity against *S.aureus* and *S.pneumoniae*. The resistance to cefuroxime was not at all similar in the seven microbiological laboratories, using the low breakpoint: *E.coli* (2 to 31%), *K.pneumoniae* (1 to 24%), *Enterobacter cloacae* (13 to 81%) and *P.rettgeri* (0 to 52%). The resistance of *Enterobacteriaceae* to cefotaxime and ceftazidime was very low in all laboratories.

Co-trimoxazole showed good activity against most of the tested strains, although a relatively wide variation was seen between the laboratories: *E.coli* (9 to 24%), *C.freundii* (1 to 21%), *S.marcescens* (0 to 22%), *Neisseria meningitidis* (2 to 78%), *M.catarrhalis* (3 to 72%), *Enterococcus* spp. (4 to 28%) and *S.epidermidis* (3 to 48%).

Gentamicin and tobramycin were active against almost all strains of *Enterobacteriaceae*.

The data from this surveillance study are difficult to interpret as they are a mixture of clinical isolates and community-acquired isolates and repeated isolates from the same patient were also included. The differences in susceptibility to second-generation cephalosporins and co-trimoxazole between the Dutch microbiological laboratories may well have a major impact on the selection of an antimicrobial agent for the treatment of sepsis with an unidentified pathogen. As stated above, these data are not readily available from most Dutch hospitals.

Drug selection

In the Dutch hospitals, a combination therapy of a betalactam antibiotic (mostly amoxycillin, ampicillin, co-amoxiclav or cefuroxime) with an aminoglycoside is the preferred regimen for most forms of sepsis. The role of third generation cephalosporins is still limited.

Most formularies use gentamicin as the aminoglycoside of choice. The activity of gentamicin and tobramycin against *Enterobacteriaceae* is usually similar but the acquisition cost of gentamicin is lower. There are no major differences in toxicity between the two aminoglycosides (12). In the Dutch hospitals these drugs are usually given twice daily, despite the fact that clinical studies with twice daily gentamicin, tobramycin or netilmicin have not been published. This is to be considered as a compromise between microbiologists and hospital pharmacists, who favour once daily administration and clinicians who prefer the conventional 3 times daily dosing (13).

In *urosepsis*, Gram-negative bacilli play an essential role (7). Most formularies recommended cefuroxime with or without an aminoglycoside. The coverage of amoxycillin or ampicillin against *Enterobacteriaceae* is incomplete, but in the Dutch hospitals gentamicin is still very active against most strains of Gram-negative bacilli.

Despite the introduction of new agents such as the fluoroquinolones, imipenem and broad-spectrum cephalosporins and penicillins, the mortality of Gram-negative sepsis has not decreased dramatically in the last 20 years (14).

Sepsis originating from the respiratory tract is often difficult to prove as infiltrations on chest X-ray are not always of infectious origin. Reliance on sputum Gram-stain and culture is an im-portant guide to antimicrobial therapy.

Most Dutch formularies provided coverage against the most likely pathogens involved in *intra-abdominal sepsis*. The recommendations for sepsis originating from the lower or upper digestive tract were similar in 14 formularies and different in 6 formularies. In three of these the main difference was the addition of metronidazole in case of sepsis originating from the lower digestive tract and in the three other formularies different antimicrobial drugs were used for the two forms of intra-abdominal sepsis. A specific anti-anaerobic drug such as metronidazole was added to the regime in more formularies in case of intra-abdominal sepsis originating from the lower digestive tract. In this case, *Bacteroides* spp. are likely to be involved in the infection (7, 9, 15). The recommendations for biliary sepsis were usually different from those for abdominal sepsis. Ten formularies provided different guidelines, whereas six formularies showed similar recommendations.

Sepsis originating from the skin or from an intravenous or intra-arterial line is most likely to be caused by *S.aureus* or *S.epidermidis*. Due to the low prevalence of methicillin-resistant *S.aureus* (MRSA) in the Netherlands, an initial choice for flucloxacillin or another antistaphylococcal penicillin is correct, although also first and second generation cephalosporins and co-amoxiclav are active against *S.aureus* (16). Strains of *S.epidermidis* are frequently resistant to many commonly prescribed antimicrobial agents, so that the empiric therapy may need to be changed when the susceptibility data are available.

The dose recommendations for flucloxacillin in the Dutch antibiotic formularies were quite variable.

Route of administration

The intravenous route was chosen by all formularies. This is logical, considering the severity of the infection and the poor clinical condition of the patient and the very limited experience with oral antibiotics in septic patients. The fluoroquinolones, such as cipro-floxacin and ofloxacin, might be given orally after 2-3 days of initial intravenous administration, but only a limited number of studies are available on this subject (17). Studies with oral cephalosporins, such as cefuroxime axetil, cefixime and cefpodoxime proxetil are also lacking (18). One formulary recommended the use of oral ofloxacin in Gram-negative sepsis, after an initial treatment with iv cefotaxime during 3 days.

Two formularies recommended continuous infusion for betalactam antibiotics. Animal studies with continuous infusion (especially in neutropenic models) suggest indeed that continuous infusion is more effective than intermittent dosing of cephalosporins or penicillins, but clinical studies are lacking (19, 20). A dose reduction of cephalosporins or penicillins in patients receiving continuous infusions seems premature, due to the lack of clinical studies.

Dosage and duration of treatment

A wide variety in dose recommendations between the formularies was observed, especially for amoxycillin. As the prognosis of severe sepsis is dependent on many factors (14, 21, 22) of which antimicrobial therapy is only one, no clear-cut guidelines for the dosage of antibiotics in sepsis can be given, also due to a lack of studies investigating the relationship between dose of antimicrobial drugs and clinical efficacy. The number of formularies that provided guidelines for the duration of treatment was limited. The recommendations (10-14 days or until 3-5 days after clinical improvement) were similar in these formularies.

Cost

An important consideration in the choice of antibacterial therapy is also the cost. Antibiotics represent about 20% of total drug costs in hospitals. The mean prices for various antibiotics are listed in Table 6.

TABLE 6

ACQUISITION COST OF PARENTERAL ANTIMICROBIAL AGENTS
Mean realistic cost, including VAT, for an average Dutch hospital

Drug	Daily dose (g)	Daily cost (NLG)
Amoxycillin	4	15
Co-amoxiclav	3 6	30
Flucloxacillin	6	38
Cefazolin	4	18
Cefuroxime	4 5	72
Cefotaxime	3	66
Piperacillin	12	110
Metronidazole	1 5	12
Gentamicin	0 24	10
Tobramycin	0 24	25

These data are quite different from the official prices, especially in case of cefazolin and gentamicin. For university hospitals and large non-university hospitals lower prices are achievable. Gentamicin, metronidazole, amoxycillin and cefazolin are the cheapest antibiotics. In the Netherlands, there is no important difference in cost between the second and third generation cephalosporins and the cost of cefotaxime is usually even lower than that of cefuroxime. The first generation cephalosporin cefazolin is considerably cheaper than the newer cephalosporins. First generation cephalosporins play a very modest role in Dutch antibiotic policy. Only two formularies recommended cefazolin or cephalothin in combination with an aminoglycoside for the initial treatment of sepsis of unknown aetiology. If first generation cephalosporins can be used for the treatment of sepsis with unknown pathogen on the basis of culture results and antibiotic susceptibility data from the hospital, considerable savings on antibiotic costs are achievable considering the average use of 3.38 Defined Daily Doses (DDD) per 100 bed days of second generation and 1.12 DDD per 100 bed days of third generation cephalosporins in Dutch hospitals (23).

CONCLUSIONS

The pathophysiology of sepsis is highly complex; antimicrobial treatment plays an important role in therapy, but many other factors are involved in the prognosis.
The guidelines for the treatment of sepsis in Dutch antibiotic formularies appear to provide coverage against the most likely pathogens involved in these infections, although substantial differences were observed in the choice of antimicrobial agents for the treatment of sepsis. Most Dutch hospitals have a "conservative" antibiotic policy and newer broad-spectrum antimicrobial agents are used to a limited extent. Dose recommendations for amoxycillin and flucloxacillin were quite variable. The formularies cannot be fully interpreted, due to the lack of data on the prevalence of causative micro-organisms and the relative susceptibility of bacteria to different classes of antimicrobial agents. Data from the Dutch surveillance study showed that the resistance of *Enterobacteriaceae* to co-trimoxazole and cefuroxime was quite variable. As a rule, the levels of resistance to cephalosporins and aminoglycosides are still low. It is impossible to give clear guidelines for the choice of antimicrobial agents, dosage and duration of treatment, because of the lack of controlled clinical studies and the fact that reliable local susceptibility patterns for the Dutch hospitals were not available. We hope that the increasing degree of automation of the microbiological laboratories will provide this information in the near future.

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CHAPTER VII

ANTIBIOTIC PROPHYLAXIS IN SURGERY IN THE NETHERLANDS
Antimicrobial prophylaxis in bowel surgery

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SUMMARY

The guidelines for antimicrobial prophylaxis in various types of bowel surgery (colorectal, biliary and gastroduodenal) in 33 Dutch antibiotic formularies, used by 89 Dutch hospitals, were studied. The majority of the formularies recommended drugs with adequate antibiotic coverage of the bacteria that are most frequently seen in surgical wound infection. Co-amoxiclav and first or second generation cephalosporins, with or without metronidazole, were most often used. The use of third generation cephalosporins and broad spectrum penicillins was low. A relatively high proportion (between 52 and 66%) of the formularies recommended multiple-dose regimens.

Most Dutch hospitals have written guidelines for the use of antimicrobial agents for the prophylaxis and therapy of infections. These antibiotic formularies reflect the views on antimicrobial therapy of the medical staff and the guidelines are usually well maintained. The formularies are specific for the hospital in question or for a number of hospitals in the same region (regional formularies).
In this study we have investigated the formulary recommendations in Dutch hospitals for the use of antimicrobial prophylaxis in bowel surgery to gain insight into the antibiotic policies in Dutch hospitals.

MATERIALS AND METHODS

By means of a letter to the members of the Dutch Association of Hospital Pharmacists, the most recent version of the antibiotic formulary, utilized in the hospital, was requested.
According to the information from the formularies received several forms of bowel surgery (colorectal, biliary and gastroduodenal) were investigated.
The following items were recorded for each surgical procedure: the number of formularies in which the given surgical procedure was included, whether or not antibiotic prophylaxis was used, the drug or drug combination of choice, dosage, route of

administration, timing of administration and the duration of prophylactic use of antimicrobials. All remarks concerning special indications or limitations to the use of antibiotics in surgery were also recorded for each individual formulary.

The antibiotic formularies were divided into two groups: Group I: formularies dating from before 1991 and Group II with formularies dating from 1991 to 1993.

RESULTS AND DISCUSSION

A total of 33 formularies as used by 89 Dutch hospitals were received. Of these, 13 were dated before 1991 and 20 were from the years 1991 to 1993.

The distribution of the formularies was as follows:

1993 (n=2), 1992 (n=12), 1991 (n=6), 1990 (n=5), 1989 (n=3), 1988 (n=1), 1987 (n=2), 1986 (n=1), 1985 (n=1).

All antibiotics were given by the intravenous route for all types of surgery. In case of multiple dosing, the dosage interval was 8 hours.

Specification of antibiotics used in colorectal surgery is given in Table 1. The first dose was given 30-60 minutes before surgery in all formularies.

Colorectal surgery was included in all formularies.

In all hospitals prophylactic antibiotics were combined with "preparation" of the gastro-intestinal tract with oral antibiotics. Specification of these drugs was usually not given.

In one formulary (dating from 1986) orthograde bowel lavage with metronidazole and neomycin was used, without systemic antibiotic coverage.

Of the six formularies in which co-amoxiclav was recommended, 4 advised a single dose of 2.2 g, 1 formulary used 3 x 1.2 g and one formulary recommended a 2.2 g dose, followed by two doses of 1.2 g. A variety of dosage-recommendations was given for the combination cefuroxime-metronidazole and even more so for the combination of gentamicin and metronidazole. Five different dosage regimens were used in the 7 formularies, where this combination was used.

TABLE 1

COLORECTAL SURGERY
Prophylactic antibiotics recommended by 33 antibiotic formularies from Dutch hospitals

	No. of formularies making recommendations Group I	Group II	Total
Duration recommended			
1 dose	1	10	11
3 doses	11	10	21
Drugs recommended			
Co-amoxiclav	1	5	6
Cefuroxime/metronidazole	3	5	8
Cefamandole/metronidazole	1	1	2
Cefazolin/metronidazole	2	2	4
Ceftriaxone/metronidazole	1	1	
Cefotetan		1	1
Gentamicin/metronidazole	4	4	8
Co-trimoxazole/metronidazole		1	1
Gentamicin/clindamycin	1	1	

Group I Formularies dating from before 1991
Group II Formularies from 1991-1993

The total gentamicin dose ranged from 2 mg/kg to 4.6 mg/kg and the metronidazole dose ranged between 500 mg and 1.5 g.

The need for prophylaxis in colorectal surgery is clear if one looks at the very high rate of wound infections without antibiotic prophylaxis (1-4). In the USA oral antibiotics such as neomycin and erythromycin base are used, often without systemic coverage with antibiotics (2). In the Netherlands this therapy is used in only one hospital.

Co-amoxiclav, cefuroxime + metronidazole and gentamicin + metronidazole are the most commonly used drugs. All regimens used in the 32 formularies provide good coverage against *Enterobacteriaceae* and anaerobes.

The choice of antibiotics for prophylaxis in colorectal surgery in The Netherlands compares favourably with a survey which was performed in 1989 in Germany (5), where correct prophylaxis (defined as good coverage against *Enterobacteriaceae* and

anaerobes, using agents that did not have an important place in the treatment of infections) was given in only 29% of the hospitals. Neither first generation cephalosporins plus metronidazole nor co-amoxiclav were used in the German hospitals.
A single dose prophylaxis was as effective as multiple dose regimens (2, 3, 6). A single dose is used in 50% of all new Dutch formularies, but in only 8% of the older formularies, which shows the increasing awareness of the efficacy of single dose regimens. A single dose was used in 43% of the German hospitals (5).

The details on the use of antibiotics, and the duration of prophylaxis in biliary surgery are given in Table 2.

TABLE 2

BILIARY SURGERY
Prophylactic antibiotics recommended by 33 antibiotic formularies from Dutch hospitals

	No. of formularies making recommendations		
	Group I	**Group II**	**Total**
Duration recommended			
1 dose	4	6	10
1-3 doses	1		1
2 doses		1	1
3 doses	4	7	11
4 doses		3	3
5 days		1	1
Drugs recommended			
Co-amoxiclav	1	7	8
Co-amoxiclav/gentamicin		1	1
Amoxycillin/gentamicin		2	2
Piperacillin		1	1
Cefazolin	2	2	4
Cefuroxime	4	1	5
Cefotetan		1	1
Cefamandole/metronidazole		1	1
Cefazolin/metronidazole	2	1	3
Gentamicin/clindamycin		1	1

Group I Formularies dating from before 1991
Group II Formularies from 1991-1993

Guidelines for antimicrobial prophylaxis were given in all formularies in which biliary tract surgery was included.
Four old and nine new formularies stated that antibiotic prophylaxis was only indicated in high-risk groups. This was specified as age above 70 years (n=7), acute cholecystitis (n=8), biliary tract obstruction (n=6), choledocholithiasis (n=5), cholangitis (n=4), reintervention (n=4), choledochotomy (n=3), icterus (n=2) and diabetes mellitus (n=2).
Two formularies specified that the prophylaxis was aimed at aerobic bowel flora and enterococci. One of these also aimed the prophylaxis at anaerobic bowel flora.
Co-amoxiclav was used in eight formularies at six different dosages, ranging from a 2.2 g single dose to 3 x 2.2 g. The presence of bacteria in bile correlates with the risk of postoperative surgical wound infections. Patients with infected bile should receive prophylactic antibiotics (7). It is not easy to identify patients at risk, but risk factors include acute cholecystitis or cholangitis, obstructive jaundice, choledocholithiasis or strictures, repeated surgery, diabetes and age greater than 70 years (2, 8). These indications are also mentioned by Dutch formularies. Similar indications for prophylaxis were included in an earlier investigation in Dutch hospitals (7).
Prophylaxis is aimed at the prevention of surgical wound infections and septic complications and it has not been proved that penetration into bile is of importance (9).
In one study (10) mezlocillin, which penetrates very well into bile, was more effective than ampicillin/gentamicin in the treatment of patients with cholangitis. Coverage of *E.coli* and *Klebsiella* spp. is most important, Although *E.faecalis* and *B.fragilis* are found as well in infected bile, first and second generation cephalosporins have proved to be effective prophylactic agents in biliary surgery, although they have no significant activity against the latter two species (2, 11). In the Dutch formularies, co-amoxiclav, cefuroxime and cefazolin were the most popular agents for prophylaxis. Co-amoxiclav was used more often in the new formularies than in the older ones. Broad-spectrum penicillins (piperacillin) were used in only one formulary. Besides its high

cost, the variable activity against *E.coli* is a disadvantage of the drug. Broad spectrum penicillins were used extensively in the German study (5).
The recommendations for the duration of prophylaxis were again variable. A single dose prophylaxis was recommended by 37% of the formularies and a triple dose regimen was used in 42% of these. In the German survey, 50% of all hospitals used a single dose regimen (5). Single dose prophylaxis appears to be as effective as multiple dose regimens, although a large proportion of comparative trials were performed with relatively long acting cephalosporins (12). A recent large-scale comparative study looking at single dose versus triple dose cefuroxime in over 1000 high-risk patients showed similar efficacy of both regimens (13).

The antibiotics used in gastroduodenal surgery, and the duration of prophylaxis, are presented in Table 3.
All formularies that included gastroduodenal surgery recommended prophylaxis.
Six out of nine old (67%) and 11 of 16 (69%) new formularies stated that prophylaxis was indicated in high-risk patients. This was specified as those with a diminished production of gastric acid (n=9), gastric haemorrhage (n=4), gastric carcinoma (n=5) and age above 70 years (n=1). Five other indications were given in one formulary each.
A similar dosage range to that seen in biliary tract surgery was used in gastroduodenal surgery.
The pattern of antibiotic use was similar to that in the prophylaxis of biliary tract surgery, co-amoxiclav, cefuroxime and cefazolin being the most commonly used drugs. A combination of these drugs with an aminoglycoside or metronidazole was used in about 30% of all formularies. Most formularies stated that prophylaxis is only indicated in high risk patients.
The Dutch policy is different from that in Germany. In the German survey a relatively high proportion of hospitals used third generation cephalosporins or broad spectrum penicillins with or without metronidazole (5).
Single-dose prophylaxis was given in 48% of all Dutch formularies. A similar percentage was seen in Germany (5).

Although comparative studies are scarce, single dose prophylaxis appears to be as effective as multiple dose schedules (2).

TABLE 3

GASTRODUODENAL SURGERY
Prophylactic antibiotics recommended by 33 antibiotic formularies from Dutch hospitals

	No. of formularies making recommendations		
	Group I	**Group II**	**Total**
Duration recommended			
1 dose	5	7	12
1-3 doses	1		1
2 doses		1	1
3 doses	3	6	9
4 doses		2	2
Choice of drugs			
Co-amoxiclav		6	6
Amoxycillin		1	1
Benzylpenicillin	1		1
Cefazolin	3	2	5
Cefuroxime	2	2	4
Cefotetan		1	1
Cefamandole/metronidazole		1	1
Cefazolin/metronidazole	1	1	2
Cefuroxime/metronidazole	1		1
Gentamicin/metronidazole	1	1	2
Gentamicin/clindamycin		1	1

Group I Formularies dating from before 1991
Group II Formularies from 1991-1993

CONCLUSIONS

Most Dutch formularies recommended drugs with proven clinical efficacy and a correct antimicrobial activity in surgical procedures. Co-amoxiclav was recommended frequently as well as first and second generation cephalosporins with or without metronidazole. A variety of dose recommendations has been found, and this illustrates the variability of the dosages used in clinical studies.

There was no consensus on the duration of the prophylaxis. Many formularies recommended multiple dose prophylaxis.

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CHAPTER VIII

ANTIBIOTIC PROPHYLAXIS IN SURGERY IN THE NETHERLANDS

Antimicrobial prophylaxis in gynaecological surgery

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SUMMARY

The guidelines for antibiotic prophylaxis in gynaecological surgery in 33 Dutch antibiotic formularies, representing 89 Dutch hospitals, were studied. All formularies recommended routine antibiotic prophylaxis in vaginal hysterectomies, whereas some formularies defined "high risk" groups that should receive prophylaxis as including abdominal hysterectomy and caesarian section. Co-amoxiclav was the drug of choice in 73% of the formularies that recommended antibiotic prophylaxis for abdominal hysterectomy, in 64% for vaginal hysterectomy and in 60% for caesarian section. The majority of formularies used a single dose: the rates for this were 73% in abdominal hysterectomy, 64% in vaginal hysterectomy and 50% in caesarian section. A single dose was used more often in new formularies (dating from 1991 to 1993) than in older formularies.

INTRODUCTION

Antimicrobial prophylaxis is considered useful in clean-contaminated surgery such as gynaecological operations.
There is no consensus on the choice of drugs, the duration of prophylaxis and the dosage of prophylactic antibiotics during gynaecological surgery (1-13).
The usefulness of prophylactic antibiotics in abdominal hysterectomy is still uncertain, although a meta-analysis combining the data from 17 prospective, randomized, blinded, placebo-controlled studies (14 of these using first and second generation cephalosporins), confirmed that antibiotic prophylaxis did reduce the infectious morbidity following elective abdominal hysterectomy (14).
Most Dutch hospitals use written guidelines for the use of antimicrobial drugs for prophylaxis and treatment of infections, and these are specific for the hospital in question or for a group of collaborating hospitals (regional formulary).
In this study, we have investigated the guidelines for the use of antimicrobial prophylaxis in gynaecological surgery in Dutch hospitals.

METHODS

In 1993, a letter was written to members of the Dutch Association of Hospital Pharmacists with a request to send to us the most recent version of the antibiotic formulary in use in the hospital in question.
After receipt of the formularies, the following types of surgical procedures were investigated:

- abdominal hysterectomy
- vaginal hysterectomy
- caesarian section

For each of these procedures, the following aspects were recorded: the number of formularies in which the particular surgical procedure was included, whether or not antibiotic prophylaxis was used, the drug or drug-combination of first choice, dosage, route of administration, timing of administration and the duration of prophylactic use of antimicrobials. All remarks concerning special indications or limitations of the use of antibiotics in surgical prophylaxis were also recorded for each individual formulary.
The antibiotic formularies were arbitrarily divided into two groups: "old" formularies dating from before 1991 and "new" formularies dating from 1991 to 1993.

RESULTS

A total of 33 antibiotic formularies were received. Of these, 13 "old" formularies were dated before 1991 and 20 "new" ones were from the period 1991 to 1993. The 33 formularies were used in a total of 89 hospitals, of which 6 were university hospitals.
Abdominal hysterectomy was included in 7/13 (54%) old formularies and in 18/20 (90%) new formularies. Prophylaxis was given in 2/7 (29%) old formularies and in 13/18 (72%) of the new ones. The choice of drugs and duration of prophylaxis is given in Table 1.

TABLE 1

ABDOMINAL HYSTERECTOMY
Prophylactic antibiotics recommended by 33 antibiotic formularies from Dutch hospitals

	Old formularies	New formularies	Total
1 dose	1	10	11
2 doses	1		1
3 doses		3	3
Choice of drugs			
Co-amoxiclav	1	10	11
Cefuroxime/metronidazole		3	3
Cefazolin/metronidazole	1		1

All drugs were given intravenously.
In the 11 formularies in which co-amoxiclav was used, the dosage of this drug-combination was a single 2.2 g dose in 8 formularies and 1 x 1.2 g; 3 x 1.2 g and 2 x 2.2 g in one formulary each. There were 3 different dosages for the combination cefuroxime + metronidazole in the 3 formularies in which this combination was used: 3 x (1.5 g cefuroxime + 500 mg metronidazole); 1 x (1.5 g cefuroxime + 1.5 g metronidazole) and 1 x 1.5 g, followed by 2 x 750 mg cefuroxime in combination with 3 x 500 mg metronidazole. Of the new formularies in which prophylactic antibiotics were given for abdominal hysterectomy, 5/13 (38%) stated that the prophylaxis should not be given routinely and that its use should be limited to "high risk" patients. A specification was given in only one formulary and it referred to diabetic and adipose patients. One formulary stated that a meta-analysis of double-blind studies on the prophylaxis in abdominal hysterectomy had shown that a significant reduction in infectious complications was obtained with prophylactic antibiotics (14). Vaginal hysterectomy was included in 8/13 (62%) of the old formularies and in 18/20 (90%) of the new ones. Prophylaxis was given in 7/8 (88%) of the old formularies and in all 18 (100%) of the new formularies. The antibiotics used in this surgical procedure are shown in Table 2. All drugs were given intravenously.

TABLE 2

VAGINAL HYSTERECTOMY
Prophylactic antibiotics recommended by 33 antibiotic formularies from Dutch hospitals

	Old formularies	New formularies	Total
1 dose	3	13	16
2 doses	1		1
3 doses	3	5	8
Choice of drugs			
Co-amoxiclav	4	12	16
Amoxycillin/metronidazole		1	1
Cefuroxime/metronidazole		3	3
Cefazolin/metronidazole	2		2
Co-trimoxazole/metronidazole		1	1
Metronidazole	1		1
Gentamicin/clindamycin		1	1

Of the 16 formularies in which co-amoxiclav was used, 10 advised a single dose of 2.2 g (2 g amoxycillin plus 200 mg clavulanic acid). Four formularies recommended a dosage of 3 x 1.2 g, whereas dosages of 2 x 2.2 g and 3 x 2.2 g were used in one formulary each. Two formularies recommended the combination of cefuroxime and metronidazole in a dosage of 1.5 g, followed by 2 x 750 mg cefuroxime + 3 x 500 mg metronidazole and one formulary used a single dose of cefuroxime and metronidazole in a dosage of 1.5 g each.

For both types of hysterectomy, the first dose of antibiotic was given 30-60 minutes before the initiation of surgery in all Dutch formularies.

Ceasarian section was included in 5/13 (38%) old formularies and in 15/20 (75%) new formularies. Prophylaxis was given in all hospitals which included this procedure in the formulary. The specification of the antimicrobial agents used in the prophylaxis are presented in Table 3.

TABLE 3

CAESARIAN SECTION
Prophylactic antibiotics recommended by 33 antibiotic formularies from Dutch hospitals

	Old formularies	New formularies	Total
1 dose	1	9	10
3 doses	4	6	10
Choice of drugs			
Co-amoxiclav	1	11	12
Cefuroxime	1	1	2
Cefoxitin	1		1
Cefuroxime/metronidazole		1	1
Cefazolin/metronidazole	2		2
Co-trimoxazole/metronidazole		1	1
Gentamicin/clindamycin		1	1

All drugs were given intravenously. Of the 20 formularies in which caesarian section was included, 11 (55%) specified that prophylaxis was only indicated in "high risk" patients. Only 3 formularies specified the "high risk" patients as a secondary caesarian section in the presence of prolonged (over 12 h) ruptured membranes.
The first dose of the prophylactic antibiotic was given immediately after clamping of the umbilical cord.

DISCUSSION

The choice of an antimicrobial drug for prophylaxis in surgery should depend on the following criteria:
- desired antimicrobial spectrum in relation to the bacterial flora present at the site of the operation.
- results of clinical studies
- side-effects
- pharmacokinetic properties
- cost
- antibiotic policy and local antibiotic resistance patterns

Desired antimicrobial spectrum

Vaginal secretions contain about 10^8 to 10^9 anaerobes/ml and about 10 fold less aerobes. The most important anaerobes are lactobacilli, peptostreptococci and peptococci and to a lesser extent also *Bacteroides* spp. (1). *Enterobacteriaceae* are usually found in much lower numbers (< 10^6/ml). Postoperative vaginal flora contains increased numbers of enterococci, Gram-negative bacilli and *Bacteroides* spp. (13).

Postoperative infections after vaginal hysterectomy are often polymicrobial. Enterococci, staphylococci, aerobic Gram-negative bacilli and *Bacteroides* spp. are the most frequently isolated organisms from wound infections. Antimicrobial prophylaxis should therefore, be targeted against these organisms.

First and second generation cephalosporins have good activity against *Staphylococcus aureus* and most Gram-negative bacilli, but only limited activity against *Bacteroides* spp. All cephalo-sporins are inactive against enterococci. Third generation cephalosporins are very active against Gram-negative bacilli, and only moderately active against *S.aureus*. They are inactive against enterococci and anaerobes.

Ampicillin and amoxycillin are very active against enterococci, but are not reliably active against all the other organisms considered above. Extended spectrum penicillins, such as mezlocillin (no longer available in the Netherlands) and piperacillin are not always effective against *Escherichia coli* and are often inactive against *S.aureus*.

Co-amoxiclav is usually effective against all micro-organisms commonly involved in surgical wound infections following abdominal or vaginal hysterectomy. The activity against *Enterobacteriaceae* is variable, but most strains of *E.coli*, *Proteus* and *Klebsiella* are suscepible to co-amoxiclav.

Results of clinical studies

Despite the fact that the antimicrobial spectra of cephalosporins and penicillins are different, little or no differences have been observed in the incidence of wound infections following hysterectomy between first, second and third generation cephalo-

sporins and penicillins (1). The incidence of postoperative infectious complications lies between 0 and 12% for all beta-lactams, with no significant differences between the drugs (1).
The most important pathogens involved in surgical wound infections are *E.coli* and *S.aureus*. Coverage of these micro-organisms is provided by first and second generation cephalosporins and by co-amoxiclav (7). It is questionable whether coverage of anaerobes, such as *Bacteroides* spp. is essential for drugs used in the prophylaxis of hysterectomy (7). Cefazolin is recommended by the American Society of Hospital Pharmacists (13). In a small-scale study, cefuroxime proved to be more effective than metronidazole, whereas the combination of both drugs was as effective as cefuroxime alone (4). On the other hand, a combination of cephacetrile and ornidazole, covering aerobic and anaerobic bacteria respectively, was more effective than either drug alone (7).
For both types of hysterectomies, a single dose, to be given 30 to 60 minutes before surgery, appears to be as effective as a multiple-dose schedule (1). Prophylaxis lasting longer than 24 h cannot be recommended (1).

Side-effects

As all cephalosporins and penicillins are usually well tolerated, especially in short term prophylaxis, development of side-effects is not a very important criterion in the selection of an agent for prophylaxis in surgery.

Cost

There are important differences in cost between various cephalosporins and penicillins, although they depend of course on the dosages employed. The cost of first generation cephalosporins, amoxycillin, ampicillin and metronidazole is relatively low in most countries. Co-amoxiclav is 2-3 fold more expensive, whereas second and third generation cephalosporins and broad-spectrum penicillins such as piperacillin are considerably more expensive. Due to the large differences in cost, this is often the most important criterion for the selection of an agent in antibiotic prophylaxis in surgery.

Pharmacokinetic properties
The pharmacokinetics of most cephalosporins and penicillins are roughly similar concerning their volume of distribution, elimination half-life and tissue penetration. If a surgical procedure lasts longer than approximately 3-4 h, effective concentrations at the operation site cannot be guaranteed for most beta-lactam antibiotics, due to their relatively short half-life of 1-2 h. An extra dose of the same drug may be necessary to avoid subtherapeutic concentrations (15).
Some cephalosporins, such as ceftriaxone, have an extended half-life, which means that tissue concentrations are maintained for longer periods. An extra dose is not necessary for this drug.

Antibiotic policy
A distinction between antibiotics used in prophylaxis and those used in therapy is desirable for logistic reasons. If prophylactic antibiotics are not (routinely) used in therapy, an unwanted prolongation of the "prophylaxis" on the hospital ward is impossible, if the drugs are not available there, but are only to be found in the operation theatre.
Some drugs, such as broad-spectrum penicillins and third generation cephalosporins, have an important place in the treatment of infections. Although no studies are available that show a clear relation between the (short term) prophylactic use of antibiotics and the development of resistance, their prophylactic use in surgery may theoretically induce the development of resistance and is therefore undesirable. For the same reason the use of aminoglycosides and fluoroquinolones in surgical prophylaxis is not recommended.
First generation cephalosporins are used only to a limited extent in general practice in the Netherlands and are very infrequently used in the treatment of infections in Dutch hospitals (16). This makes these drugs very attractive for use in prophylaxis.
In Dutch hospitals, second generation cephalosporins are used both in the treatment of infections and in surgical prophylaxis.
Co-amoxiclav is used mainly in prophylaxis, but some Dutch hospitals use the drug also in the treatment of infections (16).
The situation is quite different in other countries. In Belgium, oral

first generation cephalosporins are used on a wide scale in general practice and co-amoxiclav is used in the treatment of hospital infections on a much wider scale than in the Netherlands, resulting in a 3-4 fold higher usage of the drug in hospitals (16, 17).

GYNAECOLOGICAL PROPHYLAXIS IN THE NETHERLANDS

The need for prophylaxis in hysterectomy

The need for antimicrobial prophylaxis in vaginal hysterectomy is clear. Antibiotics, such as penicillins and cephalosporins, with or without metronidazole, result in a decreased febrile morbidity and lower incidence of wound infections in comparison with placebo (1). Prophylaxis was given in all new Dutch antibiotic formularies and in all but one of the old formularies.

The necessity of antibiotic prophylaxis in abdominal hysterectomy is still open for debate. Prophylaxis was advised routinely in 72% of all Dutch hospital formularies, independent of the year of publication. A meta-analysis of studies in abdominal hysterectomy showed that postoperative infections occurred in 19.5% of the patients in the placebo group and in 9.3% in the antibiotic-treated groups (14). Another study comparing cefuroxime + metronidazole with placebo showed no difference in the incidence of wound infections, but a significantly lower incidence of urinary tract infections was observed in the antibiotic-treated group (18).

None of the formularies that did not include abdominal or vaginal hysterectomy or caesarian section made any statements on the (absence of) usefulness of prophylactic antimicrobials for surgical procedures that were not mentioned in the formulary.

Choice and dosage of prophylactic agents in hysterectomy

The use of antimicrobial prophylaxis in gynaecological surgery in Dutch hospitals has been studied before by Wttewaal-Evelaar in 1987 (19). Of all surgeons that responded to the questionnaire, 46% used single-agent prophylaxis. This has now increased to 68% in vaginal hysterectomy. Metronidazole was the most frequently used single-agent drug in the study by Wttewaal-Evelaar (13%), followed by co-amoxiclav (12%) and piperacillin

(12%). Metronidazole and piperacillin are no longer used in the new formularies of Dutch hospitals in the present study.
Co-amoxiclav is by far the most important prophylactic agent in gynaecological surgery in the Netherlands, especially in the formularies from 1991 to 1993. Five comparative studies in gynaecological surgery have been published with this drug. Three studies employed a single 2.2 g dose (20-22) and two other studies used a dosage of 3 x 1.2 g (23, 24).
The clinical efficacy of the drug was similar to that of piperacillin and to the combinations of cefuroxime/metronidazole and cephradine/metronidazole but superior to metronidazole alone (23, 24).
The optimal dose of co-amoxiclav remains to be established. A single 2.2 g dose is relatively inexpensive and its efficacy has been documented in 3 clinical studies. The majority of Dutch hospitals that use the drug in gynaecological prophylaxis use this dose. There seems to be no clear reason for dosages such as 2 x 2.2 g and 3 x 2.2 g. These dosages have not been tested in clinical studies, are more expensive and increase the work load on the hospital wards.
It is surprising to see that first or second generation cephalosporins are not used alone (without addition of other antibiotics) in any Dutch hospital for this indication. In the U.S.A., first generation cephalosporins are considered as drugs of choice for this indication (13). From several personal communications it became clear that the lack of activity of cephalosporins against anaerobes and enterococci was the main reason to choose for co-amoxiclav.
Some hospitals use a combination of cefuroxime or cefazolin with metronidazole, in order to improve the anaerobic coverage. Again a variety of dose recommendations was observed. For all regimens of prophylaxis in hysterectomies a single dose is as effective as multiple dosage regimens (1).
The combination of gentamicin and clindamycin, as was used in one formulary for vaginal hysterectomy, cannot be recommended. Aminoglycosides should not be used as drugs of first choice in prophylaxis, because of their important place in the treatment of infections. Another, mostly theoretical, disadvantage of aminoglycosides is their possible interference with postoperative

recovery due to their action on neuromuscular transmission.
There is little doubt concerning the timing of antibiotic administration. Classen et al. (12) showed that administration in the two hours prior to surgery (in comparison with earlier or later administration) reduced the risk of surgical wound infections. All Dutch formularies state that prophylactic antibiotics in hysterectomies should be given between 30 and 60 minutes before surgery.

The need for prophylaxis in caesarian section
Postoperative infections such as endometritis and surgical wound infection are relatively common following caesarian section. The relationship between febrile morbidity and documented infections is not always completely clear (13).
The most important risk factor for the development of postoperative infections is prolonged labour in the presence of ruptured membranes. Other risk factors include frequent vaginal examinations, poor hygiene, social status, systemic illness, obesity, general anaesthesia and anaemia (13).
The need for prophylaxis in low risk women is still being debated. In a large scale study, involving over 1800 low-risk patients, Ehrenkranz et al. have shown a 5-fold reduction in the incidence of endometritis and a 3.7-fold reduction in wound infections with or without endometritis in the group receiving antibiotics in comparison with the group without systemic prophylaxis (25). The methodology of the study was not ideal, however, as case controls were used and the study was not blinded.
Similar results were obtained from a meta-analysis of the randomized controlled trials of the value of antibiotic prophylaxis in caesarian section. A 3-fold reduction in infection rates was found in the patients who were treated with an antibiotic, compared to those in the placebo-treated group (26). Many of the patients involved in this meta-analysis were relatively high-risk patients and it is not yet certain whether all patients need to receive antibiotic prophylaxis (6, 10).
This controversy is also found in the Dutch formularies. Although antibiotic prophylaxis was given in all formularies in which caesarian section was included, 55% of the formularies limited the prophylaxis to high-risk patients. This group was specified in only

3 of these 11 formularies as a secondary caesarian section with prolonged rupture of the membranes.
The timing of the administration of prophylactic antibiotics is different with caesarian section from that with hysterectomies. To minimize the exposure of the child, antibiotics are usually given after clamping of the umbilical cord. As far as is known, this does not influence the clinical efficacy of the prophylaxis (10, 13).
All the Dutch antibiotic formularies that made clear statements on the timing of administration advised starting the prophylaxis after the cord has been clamped.

Choice and duration of prophylaxis in caesarian section
The choice of antibiotics is similar to that in hysterectomies. First and second generation cephalosporins have been proved effective prophylactic agents (6, 13). The majority of Dutch formularies preferred co-amoxiclav to the cephalosporins. Although this agent is a good choice regarding its activity against the organisms involved in surgical wound infections and endometritis, we have not been able to find any study in which the efficacy of the drug in the antibiotic prophylaxis of caesarian section is documented.
As can be seen in Tables 2 and 3, most formularies used similar regimens for prophylaxis in vaginal hysterectomies and caesarian section. Some formularies recommended the use of a cephalosporin (cefuroxime or cefoxitin) without the addition of metronidazole in caesarian section.
A single dose of an antibiotic given after clamping of the cord is an effective prophylactic regimen and there are no indications that a longer prophylaxis is necessary (13). It is interesting to see that single dose prophylaxis was advised in only 20% of the old Dutch formularies but in 60% of the new ones. The number of old formularies including caesarian section (only 5) was too small to draw any conclusions from this observation.

CONCLUSIONS

Prophylaxis in gynaecological surgery is given in most Dutch hospitals. There is a consensus on the need for prophylaxis in vaginal hysterectomy and most formularies also advise giving

prophylactic agents in abdominal hysterectomy and in caesarian section, although several formularies state that "high risk" groups (without further specification) should receive antimicrobial prophylaxis.
The antibiotic used most frequently is co-amoxiclav. This drug is well documented in hysterectomies, but not in caesarian section. First and second generation cephalosporins have but a modest role in prophylaxis in the Netherlands.
The timing of prophylaxis was correct in all Dutch formularies and the majority of new formularies used a single dose regimen.

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CHAPTER IX

AMINOGLYCOSIDE MONITORING IN THE ONCE OR TWICE DAILY ERA
The Dutch situation considered

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SUMMARY

The results of an inquiry among Dutch hospital pharmacists on the monitoring of aminoglycosides are presented and the relevance of monitoring is discussed.
The vast majority of Dutch hospitals (47 of 65) use aminoglycosides in a twice daily dosage regimen, whereas 12 hospitals use a once daily dose. The timing of peak level sampling is usually 30 min after the end of an intravenous infusion of 20-30 min. Mean "therapeutic" peak levels of gentamicin were 7-13 mg/l in the once daily group, 6.4-9.6 mg/l in the twice daily group and 5-9 mg/l in the small 3 times daily group.
Little or no evidence has been published to substantiate a real therapeutic range for aminoglycosides, concerning a relationship between peak or trough levels of aminoglycosides and clinical efficacy, ototoxicity and nephrotoxicity. All studies have been performed with the conventional 3 times daily regimen. No therapeutic range can be defined yet for once daily or twice daily aminoglycosides. Monitoring of aminoglycosides may be helpful to reduce the variability in serum levels after a standard dose.

INTRODUCTION

Therapeutic drug monitoring of aminoglycosides has been a routine procedure for a prolonged period of time. Recently the use of routine monitoring of aminoglycosides has been questioned by McCormack and Jewesson (1).
The "therapeutic range" of aminoglycosides is based on a 3 times daily dosing schedule. Nowadays, in most cases the aminoglycosides are used in a once daily or twice daily manner.
An inquiry was performed among Dutch hospital pharmacists to gain insight into the monitoring of aminoglycosides in Dutch hospitals in relation to the frequency of administration.

MATERIAL AND METHODS

An inquiry was held among 95 Dutch hospital pharmacists, investigating the therapeutic drug monitoring of aminoglycosides.

Data were collected on the following items:

a) The usual dosing frequency of aminoglycosides in a patient with normal renal and hepatic function (once daily, twice daily, 3 times daily or continuous infusion).

b) Adaptation of the dose in patients with a diminished renal function: estimated creatinine clearance < 80 ml/min (lowering of the dosage, prolonging the dosage interval or a combination of both).

c) The period of time (hours) after initiating the aminoglycoside therapy at which it is usual to determine the first peak/trough levels, in relation to the estimated creatinine clearances (> 80 ml/min, 50-80 ml/min, 30-50 ml/min, 10-30 ml/min and < 10 ml/min).

d) The usual timing (min) of sampling of a peak level determination after an intramuscular injection, an intravenous injection or an intravenous infusion.

e) The "normal values" for a peak and trough level for amikacin, for gentamicin and tobramycin and for netilmicin, in relation to the usual dosing frequency in the hospital in question.

f) Literature references upon which the data mentioned under e) were based.

g) Data on the use of aminoglycosides and the number of serum level determinations were collected for nine hospitals.

The data were collected in a database program, DBase 3 (Ashton-Tate, Torrance CA; USA) and were indexed on the dosing frequency of aminoglycosides.

RESULTS

A total of 65 hospitals responded to the inquiry. Twelve hospitals used a once daily dosage regimen for aminoglycosides, 47 a twice daily and only 6 hospitals used aminoglycosides in the traditional 3 times daily way. All hospitals used gentamicin, tobramycin or netilmicin. Amikacin was not used in most hospitals.

There was no consensus in the mode of dose adaptation in the presence of renal disease. In the once daily group 7 hospitals lowered the dose, 2 hospitals prolonged the dosage interval and 3 hospitals used a combination of both. In the twice daily group only 3 hospitals lowered the dose, 22 prolonged the dosage interval and 20 used a combination of both, 2 hospitals did not answer this question. In the 6 hospitals using a 3 times daily dosage regimen, one lowered the dose, 2 prolonged the interval and 3 used the combination.

The timing of sampling in relation to the initiation of aminoglycoside therapy is shown in Table 1.

TABLE 1

TIMING OF THE FIRST SERUM LEVEL DETERMINATION AFTER THE INITIATION OF THE AMINOGLYCOSIDE THERAPY, IN RELATION TO THE RENAL FUNCTION

Timing (h)	Creatinine clearance (ml/min) >80 (number of hospitals)	50-80	30-50	10-30	<10
12	7	5	4	4	6
24	23	26	27	31	26
36	3	2	3	1	
48	15	18	16	12	10
72	8	6	7	6	5
96	1			1	2
not used				2	8
unknown	8	8	8	8	8

No significant differences were observed between the groups or when specified for the dosage frequency.
The timing of blood sampling after an intramuscular injection was 60 min in 23 hospitals and 45 min in 1 hospital, the other hospitals did not use intramuscular aminoglycosides. In 20 hospitals intravenous bolus injections of aminoglycosides were (infrequently) used; 9 hospitals used a sampling time of 30 min and 10 hospitals used a sampling time of 60 min, one hospital sampled after 15 min. Intravenous infusion, with an infusion time of 20-30 min, was the most usual mode of administration for aminoglycosides. In all 18 hospitals using a once daily or 3 times daily regimen, peak levels were determined 30 min after the termination of the infusion. There was less agreement in the (larger) twice daily group: 30 min in 35 hospitals, 60 min in 6 hospitals, 120 min in 2 hospitals and 45 min, 15 min and 10 min in one hospital each. One hospital in this group used intramuscular injections.
The "normal" therapeutic serum levels for aminoglycosides in the Dutch hospitals are shown in Table 2.

TABLE 2

NORMAL RANGES FOR PEAK (lower range, higher range and mean; mg/l) AND TROUGH LEVELS OF AMINOGLYCOSIDES IN THE NETHERLANDS

	Cmax low	Cmax high	Cmax mean	Cmin
ONCE DAILY (N=12)				
Gentamicin/tobramycin	7 0	13	10	<1 6
Netilmicin	10	16	13	<1 3
TWICE DAILY (N=47)				
Gentamicin/tobramycin	6 4	9 6	8 0	<1 6
Netilmicin	7 7	12 3	10	<2 0
3 TIMES DAILY (N=6)				
Gentamicin/tobramycin	5 0	9.0	7 0	<1 3

A variety of literature references was given upon which the therapeutic range of aminoglycosides was based. The book "Medicatiebegeleiding" (2) was mentioned by far most frequently.
The data on the use of aminoglycosides, expressed as defined daily dose (DDD/100 bed days), and the number of serum level determinations in relation to the use of aminoglycosides are shown in Table 3.

TABLE 3

AMINOGLYCOSIDE USE AND SERUM LEVEL ASSAYS IN 9 DUTCH HOSPITALS

No. of beds	DDD/100 beddays	Serum level assays per 100 beddays	Ratio DDD/serum level assays
>500	0 96	0 22	4 41
<500	0 25	0 14	1 84
<500	1 35	0 35	3 89
<500	1 80	0 47	3 81
>500	2 20	0 49	4 49
<500	0 88	0 25	3 50
<500	0 89	0 40	2 21
>500	0 72	0 17	4 15
<500	1 34	0 22	5 89
Mean	1 15	0 30	3 80

DISCUSSION

The monitoring of aminoglycosides is considered to be important because of the unpredictable serum levels after intravenous infusion and because of the relationship between peak and trough levels with clinical efficacy, ototoxicity and nephrotoxicity. Several articles have questioned the usefulness of routine monitoring of these drugs recently (1, 3). Before monitoring of a drug can be considered useful it is necessary that a relationship between peak and/or trough levels with clinical efficacy or toxicity has been shown.

RELATIONSHIP BETWEEN PEAK LEVEL AND CLINICAL EFFICACY

The relationship between aminoglycoside peak levels in serum and clinical efficacy is very difficult to investigate for a variety of reasons. Aminoglycosides are (virtually) always used in combination with broad-spectrum betalactam antibiotics, such as the penicillins and the second or third generation cephalosporins. These agents have a very good in-vitro activity against most Gram-negative bacteria, which makes it rather difficult to evaluate the efficacy of an aminoglycoside which is added to these cephalosporins.

Clearly a rigid therapeutic range of peak levels for aminoglycosides does not take into account the in-vitro sensitivity of the micro-organism, the localization of the infection and the clinical situation of the patient. If a patient is treated for a urinary tract infection, the concentrations at the site of the infection will be much higher than in case of pneumonia or meningitis. "Therapeutic levels" of aminoglycosides will not be the same if the infecting micro-organism is a *Pseudomonas aeruginosa* with a minimum inhibitory concentration (MIC) of 4 mg/l or an *Escherichia coli* with a MIC of 0.12 mg/l. Patients with a severely impaired immune function will need higher dosages and higher levels than healthy young subjects.

Several methodological problems play an important role in the interpretation of the "evidence" for a therapeutic range of aminoglycosides. The 6 studies that provide evidence of a therapeutic peak level of aminoglycosides were not randomized, prospective and blinded, while 5 of these were published > 7 years ago (1). Other antibiotics that were used in the treatment of these patients were not always clearly identified, which complicates the interpretation of the data on the efficacy of aminoglycosides in relation to peak levels. The duration of the infusion was not stated in 5 of the 6 studies. Peak serum concentrations were determined 60 min after termination of the infusion in all studies (1).

In 53 of the 65 Dutch hospitals, peak serum levels were determined 30 min after an intravenous infusion of 20-30 min, but a variety of other sampling times, such as 10, 15, 45, 60 and 120 min, were also used. In one hospital levels were determined after 2 and 6 h, and peak and trough levels were calculated by back-extrapolation. It is clear that different sampling and calculations times will result in different "peak" levels. It is important to keep in mind that the sampling time of peak levels in the Dutch hospitals (usually 30 min) deviates from the studies (60 min) on which the "therapeutic range" of aminoglycosides is based.

The sampling time after an intravenous bolus injection should be 60 min. When a sampling time of 30 min is used, this may result in relatively high "peak" levels, because the distribution may take up to 45 min (4). A relatively large proportion of UK hospitals also used a 30 min sampling time after an intravenous bolus injection (4).

Jeliffe et al. proposed sampling aminoglycoside levels immediately after the end of the infusion (most informative time for alterations in the volume of distribution) and an estimated 1.44 half-lives later (most informative time for alterations in the half-life (5).

No consensus has been obtained in the Netherlands on the sampling time in relation to the initiation of the aminoglycoside therapy. In patients with normal renal function this period of time ranges from 12 to 96 h, with most assays performed after 24 or 48 hours after the start of therapy. No clear trend towards different sampling times was observed in patients with a diminished renal function. In 8 hospitals aminoglycosides were not used in patients with a severely impaired renal function. A steady state level of aminoglycosides is reached after 5 half-lives. A steady state will therefore be reached within a day in patients with normal renal function, but this may take many days in patients with a poor renal function.

The problem with this approach is that the elimination half-life of an aminoglycoside is not known in a specific patient before serum levels have been determined. In patients with impaired renal function, the determination of serum levels before a steady-state has been reached may be useful to prevent potentially toxic levels. A determination of the peak and trough levels after 24 to 48 h will be adequate in the vast majority of patients with normal renal function.

Another very important aspect that has to be considered is the fact that the traditional peak levels of aminoglycosides are based on a 3 times daily dosage schedule. In animal experiments and in (limited) clinical trials some reduction or no change in the toxicity was observed with once daily administration in comparison with 3 times daily dosing (6). The effects of once daily or twice daily administration on the clinical efficacy appear to be similar to the conventional schedule (7-9).
Again this is difficult to study because aminoglycosides are used in combination with other antibiotics. The clinical evidence for once daily dosing of aminoglycosides is still limited, but the results appear to be encouraging (6, 10).
It is important to keep in mind that no studies have been performed on the relationship between peak levels of aminoglycosides and clinical efficacy after once or twice daily dosing. It is questionable to use the same peak levels with these schedules as with the thrice daily dosing (11). In 4 of 8 hospitals using once daily dosages of gentamicin, peak levels of 4-12 mg/l are considered as therapeutic, whereas in 4 other hospitals peak levels of 10-20 mg/l are aimed at. For the 5 hospitals using once daily netilmicin a more uniform peak level of 10-15 mg/l is used. The average range for the peak levels of twice daily gentamicin is 6-10 mg/l and only 4 of 47 hospitals use higher levels of 8-20 mg/l. Too few hospitals used amikacin to draw any conclusions for this drug.
Although it seems attractive to use three-fold higher peak serum levels for the once daily and 1.5-fold higher levels for the twice daily dosing in comparison with the conventional 3 times daily dosing, this has not been substantiated in any study. In most hospitals the "therapeutic" peak levels with once or twice daily dosing are relatively low. The rate of killing of bacteria by aminoglycosides is highly dependent on the ratio serum level/MIC. At high ratios a much higher killing rate (with less regrowth) is seen than at lower ratios (12).
In conclusion, there is very little evidence to substantiate a relationship between peak serum levels of aminoglycosides and clinical efficacy, especially with once or twice daily dosing.

RELATIONSHIP BETWEEN TROUGH LEVELS AND CLINICAL EFFICACY

In all hospitals trough levels were determined immediately prior to the next dose.
There are no prospective, controlled studies that show any relation between aminoglycoside trough levels and clinical efficacy of these drugs (1). The same methodological problems that have been described above also apply to this aspect (combination therapy, frequency of dosing, sensitivity of the micro-organism).
Aminoglycosides have a significant postantibiotic effect against Gram-negative bacteria such as *P.aeruginosa, E.coli, Klebsiella pneumoniae, Enterobacter cloacae* and *Acinetobacter calcoaceticus* (13). This permits less frequent (once or twice daily) dosing of aminoglycosides with no loss of activity. Very little data are available on the postantibiotic effect of aminoglycosides against Gram-positive bacteria, such as enterococci, pneumococci and staphylococci (13).
Again it is unlogical to use the same trough levels with once daily dosing in comparison with 3 times daily use. Yet the reported trough levels in the Dutch hospitals are not different in the once daily, twice daily and 3 times daily groups.

RELATIONSHIP BETWEEN ADJUSTING OF SERUM LEVELS AND CLINICAL EFFICACY

Few well-designed studies are available that have evaluated the effectiveness of adjusting serum concentrations of aminoglycosides to improve the clinical efficacy (14, 15). No studies of this kind have been performed with once or twice daily dosing of aminoglycosides.
Although it seems quite logical to adjust the dosage on the basis of low peak levels, a relation between dose adjustment and clinical efficacy is difficult to study, because aminoglycosides are always used in combination with other potent antimicrobial agents and because of differences in the susceptibility of the infecting micro-organisms. If no dose modifications are performed, monitoring of aminoglycosides will be useless!

RELATIONSHIP BETWEEN SERUM LEVELS AND OTOTOXICITY

Ototoxicity is the most serious complication of the use of aminoglycosides, because it is usually permanent and may cause disabling loss of hearing or impaired balance. It is usually, but not always, preceded by tinnitus or a feeling of fullness in the ears. The incidence of clinical ototoxicity ranges between 0.5 and 5% (15). Vestibular toxicity is seen most with gentamicin and auditory toxicity appears to be the highest for amikacin. Although some experimental studies suggest that netilmicin may be less toxic than other aminoglycosides, this has not been clearly demonstrated in comparative clinical studies (10).

McCormack and Jewesson have reviewed the "evidence" of a relationship between high peak or trough levels of aminoglycosides and ototoxicity (1). A total of 7 retrospective studies was evaluated. None of these studies provided clear evidence of a relationship between aminoglycoside levels and ototoxicity. A correlation was found between the duration of treatment, the number of treatment courses with aminoglycosides, the total dose of aminoglycosides given, age and pre-existing renal function impairment and the risk of developing ototoxicity. If a patient has recieved previous courses with aminoglycosides or has an impaired renal function, the use of aminoglycosides should be avoided whenever possible. There is no convincing evidence to substantiate the use of trough levels below 2 mg/l for gentamicin to prevent ototoxicity.

Again absolutely no studies have been performed that investigate the relationship between aminoglycoside peak and trough levels and ototoxicity, using a once or twice daily dosage schedule.

It is probably better to focus on a short duration of aminoglycoside therapy (3-5 days) than on specific serum levels to prevent serious ototoxicity. Daily control of early signs of ototoxicity (tinnitus, sense of fullness in the ears, headache, nausea, vertigo) may help to reduce (but not totally prevent) the risk of serious ototoxicity. If available, high tone audiograms are sensitive indicators of early hearing loss (10).

RELATIONSHIP BETWEEN SERUM LEVELS AND NEPHROTOXICITY

Nephrotoxicity of aminoglycosides is clinically less important than ototoxicity. It is usually mild and transient in nature and is almost always reversible upon discontinuation of therapy. A total of 13 studies on the relationship between aminoglycoside levels and nephrotoxicity has been reviewed (1). Some of these studies showed a significant difference between the trough levels of aminoglycosides in patients with or without relevant nephrotoxicity. This difference was much more marked in the final trough level (at the end of therapy) than in the initial trough level (at the start of therapy). In these studies it is at least as likely that the increased trough levels of aminoglycosides were caused by a reduced renal function as vice versa. No specific aminoglycoside level could be related to the development of nephrotoxicity.
As is the case with the other items, no studies have been performed to document a relationship between peak and trough levels of aminoglycosides and the risk of nephrotoxicity with once or twice daily dosage.
The best method to prevent nephrotoxicity is to minimize the duration of aminoglycoside therapy to 3-5 days and not to use these drugs in patients with pre-existing renal function impairment.
A determination of beta-2 microglobulin is a sensitive marker of early nephrotoxicity, but it is not very specific (14).
It is not completely clear whether trough levels of aminoglycosides are more informative to detect nephrotoxicity of these drugs than a routine determination of the serum creatinine level (1).

HOW TO USE AND MONITOR AMINOGLYCOSIDES?

In most Dutch hospitals, aminoglycosides have a role in the treatment of serious infections (probably) caused by Gram-negative bacteria and in the treatment of endocarditis. They are used in combination with other broad-spectrum antimicrobial agents such as the penicillins and the second or third generation cephalosporins. An attractive aspect of this combination is the fact

that aminoglycosides and betalactam antibiotics are frequently synergistic, at least in-vitro. This synergy is most marked during the first 3 days of therapy. In-vivo synergy is not as convincing as in-vitro synergy, however (10).
In most cases it will be possible to stop the use of aminoglycosides after 3-5 days and to maintain the patient on monotherapy with a broad spectrum antimicrobial drug, or (if the infective micro-organism has been identified and the sensivity pattern is known) with a specific agent.
Underdosing of aminoglycosides should be avoided if their use is considered necessary. A total daily dose of 4-6 mg/kg in one or two daily dosages is advisable in the treatment of serious infections in patients with normal renal function. If the treatment duration is limited to 3-5 days, the risk of toxicity is low (16). It is not completely clear whether the monitoring of aminoglycosides offers any benefit if these drugs are used for no longer than 5 days and in combination with other broad-spectrum antimicrobial agents.
Most Dutch hospitals (including my own) are using aminoglycosides on a twice daily basis, although virtually no literature of this dosage schedule is available! The literature on the safety and efficacy of once daily aminoglycosides is more convincing, although clinical experience is still limited. The twice daily dosage is a compromise between the well documented 3 times daily regimen and the convenient once daily regimen, because most clinicians are reluctant to use aminoglycosides once daily (personal communications).
Whenever possible aminoglycosides should be avoided in patients who run the risk for developing serious toxicity: pre-existing renal function impairment, elderly patients, recent previous treatment with aminoglycosides, ototoxic or nephrotoxic comedication, pre-existing hearing problems (17). In almost all cases monotherapy with a third generation cephalosporin or a combination with a fluoroquinolone is a possible alternative in these patients.
If a prolonged use of aminoglycosides is absolutely necessary, monitoring of these drugs might be indicated, but it must be remembered that the normal therapeutic range of aminoglycosides has not been clearly defined, especially with once or twice daily

dosing. It is advisable to aim at peak levels of at least 4-8 x the MIC of the infecting micro-organism (18). In many hospitals MICs of bacteria cultured from patients on the intensive care are routinely available. The monitoring of aminoglycosides may be helpful to reduce the variability in serum levels after a standard dose. This is especially true in children, but no studies have been published defining a therapeutic range for aminoglycosides in children. Monitoring may also be useful in patients with ascites or in patients with cystic fibrosis to avoid underdosing.
Future prospective studies on the monitoring of (once or twice daily) aminoglycosides in relationship to clinical efficacy and ototoxicity and nephrotoxicity must show whether this is a useful procedure.
It is of importance to standardise sampling times of peak and trough levels in relation to dose and duration of treatment, e.g. 30 min after the end of an intravenous infusion or 60 min after an intravenous bolus injection for peak levels and immediately prior to the next dose for trough levels, taken 24 to 48 h after the initiation of aminoglycoside therapy.

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CHAPTER X

FLUOROQUINOLONES
Use of clinical data to aid formulary choice by the System of Objective Judgement Analysis (SOJA) method

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SUMMARY

Fluoroquinolones are used in many hospitals for the treatment of complicated urinary tract infections, gastrointestinal infections, hospital acquired pneumonia and osteomyelitis. A review of the fluoroquinolones by the System of Objective Judgement Analysis (SOJA) method is presented. The following selection criteria were involved in the study: the number of registered indications, the number of dosage forms, the ratio between the area under the plasma concentration-time curve (AUC) and the MIC $_{90}$, variability of the oral bioavailability, drug interactions, dosage frequency, equal dosage for oral and parenteral use, development of resistance, clinical efficacy, adverse events, cost and documentation. Both the oral and the parenteral formulation were included in the study.
Ofloxacin shows the highest score, mostly because of the lower incidence of drug interactions, dosage frequency, cost and (relative to ciprofloxacin) a similar dosage for oral and parenteral use. Ciprofloxacin is the best documented drug. Pefloxacin shows the lowest SOJA score.
Users of this method are free to determine the relative weight of the various selection criteria that they consider to be correct, although some of the criteria are internationally valid.

Fluoroquinolones have gradually obtained an important place among the various antibiotics used in hospitals. A study conducted in 1991 demonstrated that only 16 out of 30 Dutch hospital antibiotic formularies included a quinolone (1). A study of antibiotic formularies published from 1991 to 1993 demonstrated, however, that quinolones were used in a wide range of infections. The indications for quinolones stated in these formularies are summarised in Table 1. The percentage given in the formularies for the use of a quinolone in a certain type of infection is included in this table. Not every infection is included in each formulary. As to use in uncomplicated cystitis, quinolones are recommended in a number of formularies as drugs of first choice in patients who contract cystitis in the hospital.

TABLE 1

INDICATIONS FOR FLUOROQUINOLONES IN 12 ANTIBIOTIC FORMULARIES, PUBLISHED IN 1991 TO 1993, USED IN 22 DUTCH HOSPITALS

Infection	1st choice	2nd choice
Urinary tract infections		
Cystitis	25%	17%
Pyelonephritis	8%	25%
Acute prostatitis	25%	42%
Chronic prostatitis	17%	42%
Gastrointestinal infections		
Typhoid fever	42%	8%
Salmonellosis	25%	33%
Shigellosis	17%	50%
Salmonella carriers	33%	
Travellers diarrhea	25%	8%
Sepsis		
Salmonella spp	25%	
P aeruginosa		25%
unknown aetiology		17%
Pneumonia		
unknown aetiology		17%
Gram negative bacilli		17%
P aeruginosa		25%
Osteomyelitis		
Salmonella	8%	17%
Gram negative bacilli	8%	8%
ENT infections		
Malignant otitis externa	33%	

Most formularies, however, do not recommend routine use of quinolones as drugs of first choice in general practice. Norfloxacin was mostly used in the treatment of uncomplicated cystitis. Quinolones were mainly used in complicated urinary tract infections, gastrointestinal infections, pneumonia and osteomyelitis.

A few years ago a review of possible selection criteria for fluoroquinolones was presented (2). On the basis of the current views on quinolones, a SOJA (System of Objective Judgement Analysis) score (3) has been calculated for these agents. Norfloxacin, which is only used in urinary tract infections, was not scored.

SELECTION CRITERIA

A review of the selection criteria and assigned weighting factors is presented in Table 2.

TABLE 2

SELECTION CRITERIA AND WEIGHTING FACTORS FOR FLUORO-QUINOLONES

Criterion	Weighting factor
Number of approved indications	20
Number of formulations	10
AUC/MIC$_{90}$ ratio	120
Variation in bioavailability	20
Interactions	50
Dosage frequency	60
Number of tablets/injections per day	10
Identical oral/parenteral dose	10
Development of resistance	60
Efficacy	280
Tolerability	200
Acquisition cost	100
Documentation	60
Total	1000

Number of indications

The number of registered indications is a good measure of the applicability and documentation of the quinolones. The percentage of the maximum score for approved indications was obtained as follows: Urinary tract infection (20), prostatitis (10), gonorrhoea (10), meningitis (10), respiratory tract infections (10), sepsis (10), gastrointestinal infections (10), skin/soft tissue infections (10), infections in immunocompromized patients (10).

Number of formulations

The second criterion is the number of formulations. A liquid oral administration form has advantages for patients with swallowing complaints. When various oral tablet doses are available, increasing or reducing the dosage becomes easier, without having to break tablets.

The score is obtained by adding all relevant percentages of the maximal score as follows: at least one injectable or tablet/capsule strength (60), two or more strengths (20), liquid oral form(20).

AUC/MIC ratio

The number of possible pharmacokinetic and microbiological selection criteria which could play a role in the choice of an antibiotic, is extremely high. They include bioavailability, first-pass effect, protein binding, tissue concentrations, metabolism, renal elimination, half-life, area under the plasma concentration-time curve (AUC), minimal inhibitory concentration (MIC), antimicrobial spectrum and post antibiotic effect, and many others. The relative importance of each selection criterion, however, is difficult to interpret. Pharmacokinetic and microbiological selection criteria can not be evaluated separately.

Animal experiments have demonstrated that the AUC/MIC ratio has good predictive value for the clinical efficacy of fluoroquinolones (4). A ratio of at least 40 is desirable for clinical efficacy. That is why so few separate pharmacokinetic or microbiological selection criteria have been included in this SOJA score. Instead, the AUC/MIC ratio, to which a relatively heavy weight has been assigned in the evaluation of quinolones, has been used. There are differences in tissue penetration among ciprofloxacin, ofloxacin and pefloxacin, but these are generally small and do not have any known consequences for the clinical efficacy of or resistance to these agents. Tissue penetration is, therefore, not included in the SOJA score.

Variation in bioavailability

Variation in bioavailability is the only pharmacokinetic selection criterion which is included in the score. A therapy may fail because of great differences in bioavailability and incomplete absorption. The score is based on the mean bioavailability of the fluoroquinolones after oral administration. If the bioavailability is nearly 100%, the maximal score is given for this criterion, and the relative score is proportional to the mean bioavailability. This criterion obviously does not play a role in the injection form.

Drug interactions

Drug interactions with fluoroquinolones have been described regularly in the literature. Interactions play a role only in patients who, in addition to a fluoroquinolone, are given other agents known to interact, such as theophylline, antacids, sucralfate or iron salts. The SOJA score should first be seen as a formulary decisionmaking model. Other patient-related selection criteria also play an important role in the choice of individual therapy. The evaluation of drug interactions takes into account the frequency and severity with which these interactions occur.

Dosage frequency

Dosage frequency is a great deal less important in short-term treatments, such as antibiotic treatment, than in chronic treatments, such as for hypertension. This criterion, therefore, carries a relatively lower weight than in the SOJA score for beta blockers (5). The score for the dosage frequency was determined as follows: once daily (100), once-twice daily (90), twice daily (80), 3 times daily (40), 4 times daily (10).

Number of tablets per day

In addition to dosage frequency, the number of tablets which must be taken each day also plays a (minor) role in the patient's comfort. If the daily dosage consists of 1 tablet, 100% of the maximal score is awarded. One or two tablets per day yield 90% of the maximal score, 2 tablets daily 80%; and 50% is given if more than two tablets have to be swallowed each day. A similar score is given to the number of injections which must be prepared and administered each day. In addition, 20% of the maximal score is deducted when a dose increase involves breaking tablets (for example, ofloxacin 300 mg twice daily).

Identical parenteral/oral dosage

Identical dosages in parenteral or oral use of drugs is "physician-friendly" and reduces the risk of mistakes. This criterion is not very important, which is why it is only awarded 10 points. Those preparations for which the oral and parenteral dosage is the same, are awarded 100% of this score. When the oral and parenteral dosages differ, no points are given.

Resistance development

Development of resistance is always an important selection criterion for antibiotics, although it is often difficult or even impossible to establish differences in the extent of resistance development within a group of antibiotics. The evaluation of resistance development has considered results of in-vitro studies as well as clinical resistance development in (large-scale) use of fluoroquinolones.

Efficacy

Clinical efficacy is always the most important selection criterion for any group of drugs. In general, the differences in efficacy among representatives of the same pharmacotherapeutic group are small (5-7). To evaluate this criterion, comparative studies with other antibiotics, in a wide range of infections were mainly used as well as well-designed, noncomparative studies. Comparative studies between quinolones have been very rare. Up to 280 points (100% cure for all applications) were assigned for this criterion. The score per quinolone has been established on the basis of relative cure rates in the major indications.

Adverse effects
The extent and severity of adverse effects is another important selection criterion for drugs. The importance of this criterion has been increased by the fact that the new fluoroquinolone, temafloxacin, has recently been taken off the market because of serious adverse effects, such as haemolytic uraemic syndrome and severe allergic reactions (8). The evaluation of adverse effects has been based on the results in comparative studies, the overall results in phase III and phase IV studies, and on post-marketing surveillance data. The comparison of incidence and severity of adverse effects is complicated by the fact that data from different countries cannot be compared directly. There are always fewer reported adverse effects in Japan than in Europe, and the number of adverse effects is greatest in the US (9).

Acquisition cost
The acquisition cost of antibiotics is an important criterion, because antibiotics constitute a considerable part of the total cost of drugs used in the hospital. The comparison has been based on the official wholesale prices. In case of ciprofloxacin, 250 mg tablets were used. The 500 and 750 mg tablets (on a mg basis) are much more expensive, and are not entirely reimbursed by the GVS (Geneesmiddelenvergoedingssysteem - system for the reimbursement of costs of drugs). In view of the high cost of the injection form, oral administration should be used whenever possible. The evaluation of oral administration cost has been based on the dosage generally used in systemic infections.
The cheapest oral quinolone (reimbursement price per day according to the official price list) was assigned 100% of the total score (100 points). With every 1% increase in price of a product in comparison to this agent, 1% of the maximal score is deducted. The cheapest parenteral agent was given only 40% of the maximal score, due to the relatively high cost of the parenteral formulations. For every guilder increase in cost 1% is deducted from the score.
The final cost for individual hospitals depends, however, on the bargaining results with the companies concerned. This price can differ considerably from the official price. However, this cannot be

included in the SOJA score, because these prices vary from hospital to hospital.

Documentation
It is not easy to determine a "firm" score for the documentation of a drug. The evaluation of the documentation in this score has mainly been based on the available comparative and non-comparative clinical studies, both qualitative and quantitative. Data on adverse effects and results of post-marketing surveillance have also been used, as well as available data on bacteriology, pharmacokinetics, resistance development and drug interactions.

DESCRIPTION OF THE SOJA SCORE

Number of indications
The indications for quinolones registered in the Netherlands are presented in Table 3. This table demonstrates that pefloxacin has considerably fewer indications than ciprofloxacin or ofloxacin. The evaluation of the indications is complicated by the fact that the patient package inserts of the various agents do not correspond.
On the basis of the number of indications registered, ciprofloxacin and ofloxacin are assigned 14 points (70% of the maximum score) and pefloxacin 6 points (30% of the maximum sore).

Number of formulations
On the basis of the above-mentioned considerations, ciprofloxacin, of which 3 tablet concentrations (250 mg, 500 mg and 750 mg) and two infusion solutions (100 mg in 50 ml and 200 mg in 100 ml) are available, as well as an injection concentrate of 100 mg, is assigned 10 points for the parenteral formulations and 8 points for the oral forms.
Ofloxacin, of which 200 mg and 400 mg tablets are available, as well as three infusion solutions (100 mg, 200 mg and 400 mg), is also assigned 10 and 8 points, respectively.
Pefloxacin is available as 400 mg tablets and 400 mg in 5 ml injections. Pefloxacin injection must be added to an infusion solution prior to use, thus leading to extra work and cost (10).

TABLE 3

APPROVED INDICATIONS IN THE NETHERLANDS FOR CIPROFLOXACIN (C), OFLOXACIN (O) AND PEFLOXACIN (P).

Indication	C	O	P
Urinary tract infections	+	+	+
Renal Infections		+	
Gonorrhoea	+	+	+
Lower respiratory tract infections	+	+	
Higher respiratory tract infections, caused by *P aeruginosa*	+		
Gastrointestinal infections	+		
Shigella dysentery	+	+	
Serious *S typhi* infections	+	+	
Sepsis		+	
Skin and soft tissue infections	+		
Infection prophylaxis in patients with granulocytopenia	+		

Pefloxacin is therefore assigned 6 points for both the oral and parenteral form.

*AUC/MIC$_{90}$ ratio*4
The AUC/MIC$_{90}$ ratio for the 3 fluoroquinolones is presented in Table 4. Some differences obviously exist in both pharmacokinetics and in-vitro activity. The values presented in Table 4 are mean values of several studies, in which all 3 quinolones were studied simultaneously (11-20).
An AUC/MIC ratio of 40 or higher has been associated with good clinical efficacy, whereas lower ratio may result in a higher incidence of therapeutic failures (21).

TABLE 4

AREA UNDER THE PLASMA CONCENTRATION-TIME CURVE TO MINIMUM CONCENTRATION INHIBITORY TO 90% OF TESTED STRAINS (AUC/MIC_{90}) RATIO FOR CIPROFLOXACIN (C), OFLOXACIN (O) AND PEFLOXACIN (P)

Pathogen	C	O	P
Citrobacter spp	80	40	30
Enterobacter spp	40	40	60
Escherichia coli	80	80	60
Klebsiella spp	80	80	60
Proteus spp	160	160	120
Providencia spp	40	20	30
Salmonella spp	320	160	240
Serratia spp	40	40	60
Shigella spp	320	160	480
Haemophilus influenzae	640	640	960
Neisseria gonorrhoe	1280	1280	1920
Pseudomonas aeruginosa	20	10	15
Staphylococcus aureus	10	20	30
Streptococcus pneumoniae	5	10	4
Enterococcus faecalis	5	5	8

The AUC/MIC ratio following oral administration of ofloxacin is somewhat lower than that of pefloxacin and ciprofloxacin for a number of *Enterobacteriaceae*.
The differences are usually not very clinically relevant, because the AUC/MIC ratio for the majority of bacteria is very high except for *Providencia* spp. and *P.aeruginosa*. The AUC/MIC ratio of all quinolones for Gram-positive bacteria is considerably lower than

that for *Enterobacteriaceae*. Ofloxacin scores similarly or better than ciprofloxacin for these bacteria.
None of the fluoroquinolones shows an ideal AUC/MIC ratio, the ratio for *Providencia spp., Serratia spp.* , *P.aeruginosa* and Gram-positive cocci is relatively low. On the basis of these numbers, ciprofloxacin and pefloxacin are awarded 75% of the maximal score (90 points), and ofloxacin 70% of the maximal score (84 points).
The situation is different for parenteral administration. The registered parenteral dosages, especially for ciprofloxacin, are relatively low in comparison with those used in other countries. The AUC/MIC ratio of 200 mg twice daily ciprofloxacin intravenously is lower than the score with 500 mg twice daily orally. Compared to the bioavailability of approximately 70% of oral ciprofloxacin, the AUC/MIC ratio of the intravenous form is lower than the oral form by almost a factor of 2.
Intravenous pefloxacin scores the highest, followed by ofloxacin. The AUC/MIC ratio is almost identical to the ratio following oral administration. Ciprofloxacin has the lowest AUC/MIC ratio. Pefloxacin scores 75% (90 points) for this criterion, ofloxacin 70% (84 points) and ciprofloxacin 60% (72 points).

Variation in bioavailability
Both ofloxacin and pefloxacin are absorbed almost completely; bioavailability is between 90 and 100%. The bioavailability of ciprofloxacin shows greater variation; mean bioavailability is between 50 and 85% (17-20). The importance of the lesser bioavailability of ciprofloxacin is, as far as is known, not very great. No mention has been made that treatment with ciprofloxacin has failed because of insufficient absorption, except for when interactions have occurred with antacids, for example.
Ofloxacin and pefloxacin score 100% (20 points) for this criterion, and ciprofloxacin 75% (15 points). It goes without saying that all agents score 100% (20 points) if administered intravenously.

Drug interactions
Drug interactions which may occur with fluoroquinolones are summarised in Table 5.

TABLE 5

DRUG INTERACTIONS

Drug	C	O	P
Theophylline (Th)			
Decrease in Th clearance	18-32%	4-12%	18-31%
Increase in Th AUC	22-86%	4-11%	19-87%
Caffeine (Ca)			
Decrease in Ca clearance	36-46%	0%	----
Increase in Ca AUC	60-65%	0%	---
Antacids			
Reduction in bioavailability of quinolone	84-91%	22-66%	55%
Iron salts			
Reduction in bioavailability of quinolone	42-63%	11-36%	---
Calcium salts			
Reduction in bioavailability of quinolone	0-36%	0%	---
Sucralfate			
Reduction in bioavailability of quinolone	90-95%	60-70	----

Compiled from references 22-26

C ciprofloxacin O ofloxacin
P pefloxacin --- no data avalable

The degree of the interaction between either ciprofloxacin or pefloxacin with theophylline varies greatly and also depends on the quinolone dosage.
Milk and yoghurt do not affect the absorption of ofloxacin (27), but the bioavailability of ciprofloxacin was reduced by 30-36% when these dairy products were taken simultaneously (28).
In Japan a number of cases have been reported in which convulsions occurred following the use of enoxacin with the fenbufen (neither agent is available in the Netherlands). This effect was most pronounced with enoxacin and least pronounced with ofloxa-

cin (of the quinolones discussed in this article) (29). Within the framework of post-marketing surveillance, possible interactions of ofloxacin with various NSAIDs were studied. There is so far no evidence of an increased risk of adverse effects on the central nervous system of ofloxacin and NSAIDs used in combination (30).

No detailed information is available on ciprofloxacin and pefloxacin, but so far, there is no indication of a clinically relevant interaction with NSAIDs.

On the basis of its more favourable interaction profile, ofloxacin is awarded 80% of the maximal score (40 points). Ciprofloxacin scores 50% of the maximal score (25 points), its interactions being more numerous and more serious. Relatively few data on pefloxacin are available. On the basis of the disadvantage of doubt, pefloxacin also scores 25 points.

Interactions with antacids, iron salts and sucralfate do not play a role following iv administration. Ofloxacin has no relevant interactions following iv administration and scores 100% (50 points). Ciprofloxacin and pefloxacin score 80% (40 points).

Dosage frequency

The recommended dosage frequency of ofloxacin is once daily. The once daily dosage of ofloxacin, however, has not yet been approved for all indications. It has only been approved for mild to moderate respiratory infections and uncomplicated urinary tract infections. The other two quinolones should be administered twice daily. A twice daily dosage of ofloxacin is used in most clinical studies. Since ofloxacin is usually given twice daily in practice, despite the fact that once daily dosing has been approved, ofloxacin is awarded 90% (54 points). Both ciprofloxacin and pefloxacin score 80% (48 points) for this selection criterion.

Number of tablets per day

Because in the Netherlands the price of 500 mg and 750 mg ciprofloxacin tablets is a great deal higher in comparison with the same daily dose in 250 mg tablets, a twice daily dosage of two 250 mg tablets is generally used. The daily dose of ofloxacin (400 mg) can be taken as one single tablet in respiratory infections and

urinary tract infections. The daily pefloxacin dose (800 mg) can be taken in two tablets. Conversely, higher dosages are often used in more serious infections; 750 mg twice daily ciprofloxacin or 300 mg twice daily ofloxacin, for example. In this case, ciprofloxacin again has an advantage over the other agents, because the tablets do not have to be broken. Ofloxacin is awarded 70% (90% minus 20% for breaking tablets) of the total score (7 points) for this criterion, pefloxacin 60% (6 points) and ciprofloxacin 50% (5 points) on this basis.
Ofloxacin may be given as a single injection of 400 mg, although the experience with this form is still limited. Two injections must be given for ciprofloxacin and pefloxacin. Ofloxacin scores 90% (9 points) for the parenteral form, whereas the other quinolones are awarded 80% (8 points).

Identical parenteral/oral dosage
The oral and parenteral dosages of both ofloxacin and pefloxacin are identical. Both agents score 100% (10 points). The parenteral dosage of ciprofloxacin differs from the oral dosage. It is noteworthy that the parenteral dosage (200 mg twice daily) is relatively low compared to the oral dosage of 500 mg twice daily. The bioavailability of oral ciprofloxacin is on average 70%. This is also expressed by a relatively low AUC/MIC_{90} ratio for the parenteral dosage. Ciprofloxacin scores no points for this criterion.

Development of resistance
Because of the rapid development of resistance as often occurs with nalidixic acid, much attention has been paid to the possible development of resistance to the fluoroquinolones during their development.
Quinolones have the advantage that plasmid-bound resistance development does not occur. If resistance occurs, it is often caused by chromosomal mutations.
The two major resistance mechanisms against fluoroquinolones are changes in bacterial DNA gyrase and in the extent of penetration into the bacterial cell. The first resistance mechanism leads to high-level resistance and full cross-resistance among the fluoroquinolones themselves (31). The second mechanism often

leads to a relatively low-level resistance and possibly also to the development of cross-resistance with betalactam antibiotics (32).
The frequency of spontaneously resistant mutants of *Enterbacteriaceae, P.aeruginosa* and *S.aureus* at a quinolone concentration of 4-10 times the MIC is < 10^{-8}. Substantial differences in the frequency of spontaneous mutants among ciprofloxacin, ofloxacin and pefloxacin do not appear to exist (16, 33, 34). Large-scale use of fluoroquinolones in human and veterinary infections has led to a slow but steady increase in resistance against these agents. Thus, the introduction of enrofloxacin (a derivate of ciprofloxacin) in the poultry sector was accompanied in our country by an increase in resistance of *Campylobacter* spp. to fluoroquinolones in both poultry and human isolates (35).
Initially, resistance development in hospitals mainly involved *S.aureus* and *P.aeruginosa* (36). However, more resistant *Enterobacteriaceae* are increasing gradually, especially in Southern Europe, but also in countries in which fluoroquinolones are used on a large scale in general practice, such as in Germany (37, 38).
A restrained use of quinolones in infections which can also be treated with other groups of antibiotics, such as uncomplicated urinary tract infections or bronchitis, for example, is recommended in order to prevent increased resistance development.
There are no indications of mutual differences in the extent of resistance development among ciprofloxacin, ofloxacin or pefloxacin. All agents therefore score 70% of the maximal score (42 points) for this selection criterion.

Efficacy
The clinical efficacy of fluoroquinolones has been demonstrated in numerous comparative and non-comparative clinical studies. The number of studies with ciprofloxacin especially, is impressive.
Not all infections were included in the clinical efficacy evaluation. The efficacy of all fluoroquinolones is very high in uncomplicated lower urinary tract infections and there are no differences in efficacy among the various agents. In addition, fluoroquinolones are not drugs of choice for this indication.
The results of the treatment of infections with fluoroquinolones are summarized in Table 6.

TABLE 6

REVIEW OF CLINICAL EFFICACY

	Ciprofloxacin Cure rates clin	bact	Ofloxacin Cure rates clin	bact	Pefloxacin Cure rates clin	bact
Lower respiratory tract infections	88%	83%	88%	81%	82%	81%
Cystic fibrosis	94%		93%			
Osteomyelitis		57-84%		76-86%		86%
Complicated urinary tract infections	73-91%	75-97%		75%	86%	
Prostatitis	58-80%	75-100%	70%			
Gonorrhoea		100%		100%		100%
Chlamydia infections		46-72%		95%		
Skin/soft tissue infections	77%	78%	87%	92%	76%	68%
Typhoid fever	97%		100%		96%	

clin clinically cured or markedly improved
bact bacteriologically cured: eradication of the infecting micro-organism

From references 39-84

Although there are great differences in the number of clinical studies done with ciprofloxacin or pefloxacin, there are no significant differences in clinical efficacy among the 3 quinolones, with the single exception of ofloxacin which is more effective in the treatment of Chlamydia infections. This indication, however, is not an important indication for quinolones. On the basis of the results in the infections presented in Table 6, all quinolones are awarded 85% of the maximal score (240 points).

Adverse effects

The adverse effect profiles of ciprofloxacin and ofloxacin have been extensively documented in both phase III and phase IV studies. The methodologies of both studies were comparable. General practioners and specialists were asked to complete questionnaires on efficacy and adverse effects in order to learn about their prescribing habits. No such study has been done with pefloxacin (85).

The adverse effects of ciprofloxacin, ofloxacin and pefloxacin during phase III studies have been summarized in Table 7 as well as phase IV studies of ciprofloxacin and ofloxacin. These numbers cannot be compared directly due to dosage variation and the countries in which the studies were done.

TABLE 7

ADVERSE EFFECTS (%) OF CIPROFLOXACIN (C), OFLOXACIN (O) AND PEFLOXACIN (P) DURING PHASE 3 AND PHASE 4 STUDIES

	C	C	O	O	P
No. of patients	9,473	12,404	13,717	28,889	1,181
Phase	3	4	3	4	3
Dose (g)	0.2-2		0.3-0.6		0.8
Gastrointestinal	4 2	4 7	1 9	5 2	5.6
CNS	1 4	1.4	0.7	2 9	0.9
Cardiovascular	0.2	0 4	0.1	0.2	
Skin	1 1	0.8	0 4	1.0	2.2
Metabolic	4 4				
Miscellaneous	1.6	2 9		0 3	

The use of fluoroquinolones in children is still limited, because cartilage abnormalities were found in young dogs (86).

Studies in children concentrate, therefore, on effects on cartilage. Adverse effects in children are best documented for ciprofloxacin. Adverse effects occurred in 12.6%. Arthralgia occurred in 8 of 634 children under 18 years (1.3%) (87). None of 37 children with mucoviscoidosis treated with ofloxacin developed arthralgia. Arthralgia occurred in 9 of 63 children treated with pefloxacin (85).

Although the adverse effect profiles of the quinolones are not identical, there are no indications of major differences in degree or incidence of adverse effects between ciprofloxacin and ofloxacin.

Much less data are available on pefloxacin. It appears from the limited data that skin reactions in adults and arthralgia in children occur more frequently with pefloxacin than with ciprofloxacin or ofloxacin.
The number of comparative studies of the individual quinolones is too small and the studies are too small-scale to permit conclusions about relative tolerance.
Ciprofloxacin and ofloxacin are awarded 70% of the maximal score (140 points) and pefloxacin 65% (130 points) for this selection criterion, due to the somewhat higher incidence of side effects and the poorly documented side-effects profile.

Acquisition cost
The daily price (reimbursable price according to KNMP Taxe) of the three quinolones is presented in Table 8.
Oral ofloxacin and pefloxacin are equally expensive.
Ciprofloxacin, given as two 250 mg tablets twice daily, is more expensive by NLG 1,67 per day. When 500 mg tablets are used, the difference is much greater.

TABLE 8

DAILY COST (NLG)

Ciprofloxacin	two 250 mg tablets twice daily	9 92
	one 500 mg tablet twice daily	12 32
	200 mg IV twice daily	118 92
Ofloxacin	two 200 mg tablets daily	8 26
	400 mg IV daily	116 10
Pefloxacin	one 400 mg tablet twice daily	8 26
	400 mg IV twice daily	125 30*

* including NLG 6 00 voor infusion fluid

The oral administration form of ofloxacin and pefloxacin is awarded 80% (80 points) and ciprofloxacin, which costs 20% more scores 60% (60 points).
The parenteral form of the fluoroquinolones is very expensive (relatively speaking), when compared with the oral form. The differences in cost of the parenteral formulations are very small, certainly in proportion to the high cost. Pefloxacin is only available as a 400 mg dose, which is a disadvantage when higher dosages must be used. In addition, it must be added to an infusion solution prior to use. A supplement of NLG 6.00 per day has been added to the cost for this. This cost of the 100 mg injection of ofloxacin is half the price of the 200 mg injection form. The 100 mg form of ciprofloxacin is relatively expensive: NLG 35.00 per injection vs. NLG 29.50 for ofloxacin. Ofloxacin injection is awarded 40% (40 points), ciprofloxacin injection 37% (37 points), and pefloxacin injection 30% (30 points).

Documentation

• Oral administration

The number of comparative studies between ciprofloxacin, ofloxacin and/or pefloxacin is very small, making a direct comparison of their relative efficacy and tolerability impossible. Documentation on ciprofloxacin is impressive. It largely surpasses the other two quinolones, especially pefloxacin, in the number of bacteriological as well as clinical studies. As ciprofloxacin is often considered to be the standard quinolone in in-vitro studies as well as in clinical studies, the documentation on this agent increases even more. Ciprofloxacin shows, therefore, the highest score, 95% of the maximal (57 points).
Ofloxacin is also well documented, but not to the same extent as ciprofloxacin. The clinical documentation is lacking with regard to the use of ofloxacin in nosocomial pneumonia, mucoviscidosis, gastrointestinal infections, sepsis and malignant otitis externa. Ofloxacin is the most extensively documented agent of the three with regard to adverse effects. Ofloxacin scores 80% of the maximal score (48 points) for documentation.
Pefloxacin is the least documented of all three quinolones. Its

documentation is of less value than that of ciprofloxacin or ofloxacin in all fronts. This is also manifest by the limited number of approved indications for pefloxacin. The clinical documentation of pefloxacin especially, clearly leaves room for improvement. There are still insufficient data available on its efficacy in respiratory infections, mucoviscidosis, osteomyelitis, prostatitis, Chlamydia infections, skin and soft tissue infections and gastrointestinal infections. In addition, the post-marketing surveillance of adverse effects leaves much to be desired in comparison with the other two drugs. Pefloxacin scores 30% (18 points) for documentation.

• Parenteral administration

There is less documentation on the parenteral forms than on the oral forms. The number of studies and the number of patients treated is only a fraction of the number for oral administration.
All three quinolones are arbitrarily awarded 10% less than for the oral administration: ciprofloxacin 51 points, ofloxacin 42 points and pefloxacin 9 points.

CONCLUSIONS

The SOJA scores of the oral and parenteral administration forms of the quinolones are presented in Tables 9 and 10.
The scores for the oral dosage forms are higher than those for the parenteral formulations, due to the higher cost and the poorer documentation of the injections in comparison with the oral forms.
Ofloxacin scores higher than the other two quinolones, because of drug interactions, dosage frequency, acquisition cost and (with regard to ciprofloxacin) identical oral and parenteral dosage.
The advantage of ciprofloxacin is excellent documentation. In addition, ciprofloxacin has a favourable score compared to pefloxacin with regard to the number of approved indications and the number of formulations. Pefloxacin does not have any marked advantages or disadvantages over the other quinolones. Pefloxacin looses points especially with regard to documentation and, as a result, number of approved indications.

TABLE 9

SOJA SCORE FOR ORAL FLUOROQUINOLONES

Criterion	C	O	P
Number of approved indications	14	14	6
Number of formulations	8	8	6
AUC/MIC_{90} ratio	90	84	90
Variation in bioavailability	15	20	20
Interactions	25	40	25
Dosage frequency	48	54	48
Number of tablets per day	5	7	6
Identical oral/parenteral dose	0	10	10
Development of resistance	42	42	42
Efficacy	240	240	240
Tolerability	140	140	130
Acquisition cost	80	100	100
Documentation	57	48	18
Total	**764**	**807**	**741**

The score presented here is specific for the Dutch situation. To make it more internationally applicable, the scores have been expressed as a percentage of the maximal score. Of course, every user of this method is free to determine the relative weight of the various selection criteria considered to be correct. Several criteria are internationally valid: AUC/MIC ratio, variation in bioavailability, drug interactions, identical oral and parenteral dose, development of resistance, efficacy, tolerance and documentation. Other criteria are country and time-dependent: number of approved

indications, number of formulations, dosage frequency, number of dosage units per day and cost.
On the basis of these results, our hospital has decided to use ofloxacin as the fluoroquinolone of choice.

TABLE 10

SOJA SCORE FOR PARENTERAL FLUOROQUINOLONES

Criterion	C	O	P
Number of approved indications	14	14	6
Number of formulations	10	10	6
AUC/MIC_{90} ratio	72	84	90
Variation in bioavailability	20	20	20
Interactions	40	50	40
Dosage frequency	48	54	48
Number of vials per day	8	9	8
Identical oral/parenteral dose	0	10	10
Development of resistance	42	42	42
Efficacy	240	240	240
Tolerability	140	140	130
Acquisition cost	37	40	30
Documentation	51	42	9
Total	**722**	**755**	**679**

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CHAPTER XI

SEQUENTIAL THERAPY WITH INTRAVENOUS AND ORAL CEPHALOSPORINS

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SUMMARY

The pharmacokinetic, economic and practical aspects of sequential therapy with iv and oral cephalosporins are reviewed. New broad spectrum oral cephalosporins, such as cefixime, cefpodoxime proxetil and cefetamet pivoxil achieve serum concentrations above the MICs for most *Enterobacteriaceae* for at least as long as is for parenteral cefuroxime. Substantial cost reductions are possible with an early switch from iv to oral cephalosporins. The clinical studies that have been performed so far have important shortcomings. Well designed clinical studies are necessary to prove the feasibility of sequential therapy with cephalosporins for serious infections in hospitalised patients.

INTRODUCTION

It is common hospital practice to start antimicrobial therapy of serious infections with iv antibiotics. Most clinicians change to oral antibiotics as soon as the condition of the patient is improved and oral treatment is possible, a practice which may be referred to as sequential, step-down or follow-on therapy. Drugs such as amoxycillin, flucloxacillin, co-trimoxazole, fluoroquinolones and doxycycline may be used in this way. Oral bioavailability of the latter three agents is high. Both penicillins however are incompletely absorbed after oral administration, for amoxycillin 75% in healthy subjects, but less effectively in ill patients and for flucloxacillin, 55%. Furthermore the oral doses (usually 500 mg 3 times daily) may be lower than intravenous dosage (1 g 4 times daily), despite their incomplete absorption. Higher oral dosages are poorly tolerated. Very few studies have investigated the safety and efficacy of sequential therapy with penicillins or other antibiotics. The few studies that have been published were performed in children (1-3).

Several potent oral cephalosporins, such as cefuroxime axetil, cefpodoxime proxetil and cefixime have recently been introduced. These drugs have a good in-vitro activity against a broad range of Gram-negative bacteria and are therefore potentially useful as a sequential oral therapy following treatment with intravenous cephalosporins, such as cefuroxime and cefotaxime. In this article the theoretical and practical aspects of such therapy and clinical implications are reviewed.

PHARMACODYNAMIC CONSIDERATIONS

Betalactam antibiotics have almost always been given as intermittent doses. This concept was based on the idea that some bacterial regrowth was necessary to obtain bactericidal activity. Therefore, the usual dosage schedules for most of these antimicrobial agents were 3 or 4 times daily, despite the relatively short half-lives of the penicillins and cephalosporins.

This traditional approach to the antibacterial action of betalactams is now being questioned. It has become clear from animal experiments that the most reliable predictor of betalactam in-vivo activity is the period during each dosage interval when the antibiotic serum concentration exceeds the MIC for the infecting micro-organism (4). The very high initial serum concentrations obtained after iv injection do not seem to contribute to the in-vivo activity of betalactams. The rate and extent of bactericidal activity of betalactam antibiotics apparently do not greatly improve with increasing concentration, provided that MICs for pathogens are exceeded. Also, betalactam antibiotics do not possess a marked post-antibiotic effect against *Enterobacteriaceae*, and therefore these bacteria will start to multiply almost immediately after the serum concentration has fallen below the MIC.

In treatment of *Klebsiella* pneumonia in neutropenic rats, Roosendaal et al. (5) showed that a continuous infusion of ceftazidime was much more effective than the same daily dose given as three iv injections. Interpretation of these results, must take into consideration that the half-life of ceftazidime in rats (30 min) is much shorter than in man.

The potential of sequential therapy with iv followed by oral cephalosporins depends on the pharmacodynamics of iv and oral cephalosporins, in particular that the serum concentration should exceed the MICs for most common pathogens over a 24 h period. These data are presented in Tables 1 and 2.

TABLE 1

MIC$_{50}$ OF CEPHALOSPORINS

	Cefuroxime	Cefpodoxime	Cefixime	Cefetamet	Cefotaxime
E coli	2	0 25	0 25	0 5	0 06
Klebsiella spp	2	0 12	0 06	0 12	0 06
Enterobacter spp	4	1	1	2	0 25
Citrobacter	2	1	1	1	0 25
Serratia	64	2	0 5	1	0 5
Shigella	2	0 25	2	0 25	0 12
P mirabilis	2	0 06	0 03	0 06	0 06
P vulgaris	64	0 03	0 03	0 12	0 06
M morganii	64	0 5	2	1	0 5
Providencia spp	2	0 12	0 03	0 06	0 06
Salmonella	2	0 25	0 12	0 5	0 12
Yersinia	4	1	4	1	0 5
H influenzae	1	0 06	0 12	0 12	0 03
M catarrhalis	0 5	0 25	0 12	1	0 06
S aureus	1	2	16	32	1
S pyogenes	0 008	0 008	0 5	0 06	0 06
S pneumoniae	0 015	0 03	0 5	0 25	0 03

From references 6-10

Comparison of iv and oral antibiotics in this way is preferred to the AUC/MIC ratio, which is usually much higher after iv administration, or the peak serum concentration/MIC ratio, which is also much higher after parenteral administration and is not predictive of the in-vivo effects (4).

The period per 24 h during which the serum concentration exceeds MICs for most pathogens is longer for the new extended spectrum oral cephalosporins than for iv cefuroxime and similar to iv cefotaxime. All new oral cephalosporins, except cefuroxime axetil have limited activity against *Staphylococcus aureus*. The period per 24 h during which the serum concentration of cefuroxime exceeds MICs is especially short for *Serratia*, *Proteus vulgaris* and *Morganelli morganii*. Activity against *Enterobacteriaceae* does not persist beyond 15 h per day, even after iv administration.

TABLE 2

TIME (HOURS) THAT THE SERUM CONCENTRATION IS ABOVE THE MIC$_{90}$

	Cefu 750 mg iv 3 times daily	Cefu 500 mg orally 2 times daily	Cefpo 200 mg orally 2 times daily	Cefix 200 mg orally 2 times daily	Cefetamet 1 g orally 2 times daily	Cefotaxime 1 g iv 3 times daily
E coli	15	10	23	24	24	24
Klebsiella spp	15	10	24	24	24	24
Enterobacter	11	6	12	13	16	24
Citrobacter	15	10	12	13	22	24
Serratia	1	0	7	21	22	24
Shigella	15	10	23	4	24	24
P mirabilis	15	10	24	24	24	24
P vulgaris	1	0	24	24	24	24
M morganii	1	0	17	4	22	24
Providencia	15	10	24	24	24	24
Salmonella	15	10	23	24	24	24
Yersinia	11	6	12	0	22	24
H influenzae	19	14	24	24	24	24
M catarrhalis	24	19	23	24	22	24
S aureus	19	14	7	0	0	22
S pyogenes	24	24	24	21	24	24
S pneumoniae	24	24	24	21	24	24

From references 11-15

CEFIX cefixime
CEFPO cefpodoxime proxetil
CEFU cefuroxime

EFFECTS OF FOOD ON THE ABSORPTION OF ORAL CEPHALOSPORINS

The bioavailability of cefuroxime axetil is increased by food. The absolute bioavailability of 500 mg cefuroxime axetil was 52% when taken together with food and 36% in the fasting state (16). The oral bioavailability of cefpodoxime proxetil is increased by 30% when the drug is taken with food (17), whereas the absorp-

tion of cefixime is unaffected by food (18). The bioavailability of cefetamet is increased by 20% when the drug is taken 1 h after food in comparison with administration before food or together with food (19). No studies on the effects of food on absorption of cephalosporins have been performed in moderately or severely ill patients. It is clear that such studies are needed.
When these oral cephalosporins are used as a follow up of intravenous cephalosporins, it is recommended that they should be taken with food or one h after food.

PLACE OF INJECTABLE CEPHALOSPORINS IN THERAPY

Most Dutch hospitals have antibiotic formularies, offering guidelines for antimicrobial therapy in each hospital. We have collected 15 of these antibiotic formularies, which are used in 27 hospitals in the Netherlands. An overview of the indications for second and third generation cephalosporins in these hospitals is given in Table 3. Besides these indications, cephalosporins are also used for the treatment of gonorrhea and in antibiotic prophylaxis in surgery. For these indications a single dose is usual and therefore an oral follow up is not necessary.
Possible applications of sequential therapy include hospital-acquired pneumonia, pneumonia caused by Gram-negative bacilli, sepsis of unknown origin, sepsis caused by Gram-negative bacilli, urological sepsis, pyelonephritis and arthritis caused by Gram-negative bacilli.

ARGUMENTS FOR A SEQUENTIAL THERAPY

The switch from parenteral to oral medication not only offers the recovering patient more freedom of movement, but also prevents the occurrence of infusion-related side-effects (such as thrombophlebitis), reduces hospital stay, lowers the clinical workload, reduces the amount of hospital waste and leads to considerable savings in purchase and administration of antibiotics.
A switch from iv to oral antibiotics may also result in a shorter hospital stay. In Israel the introduction of cefuroxime axetil

reduced hospital stay of patients with lower respiratory tract infections by 3.6 days compared to a historical control (20).
The workload of hospital wards is reduced because dispensing oral tablets takes much less time than the administration of injectable antibiotics.

TABLE 3

INDICATIONS (EXPRESSED AS THE PERCENTAGE OF THE NUMBER OF FORMULARIES IN WHICH THIS INDICATION IS INCLUDED) FOR CEPHALOSPORINS IN 15 DUTCH ANTIBIOTIC FORMULARIES (27 HOSPITALS)

Indication	2nd generation	2nd generation + aminoglycosides	3rd generation	3rd generation + aminoglyosides
Hospital-acquired pneumonia	27%	27%	14%	14%
Pneumonia, Gram-negative bacilli	20%	7%	20%	
Sepsis of unknown origin		60%	13%	13%
Sepsis, Gram-negative bacilli	7%	60%	20%	13%
Urological sepsis		27%	13%	
Meningitis unknown pathogen			27%	
Meningitis, Gram-negative bacilli			40%	13%
Pyelonephritis	27%		13%	
Peritonitis		27%		
Arthritis Gram-negative bacilli	7%		13%	

An important argument for a sequential therapy is the much lower cost of oral cephalosporins compared with parenteral cephalosporins. Gyssens et al. (21) made a detailed study of all the costs involved in the purchase, distribution, preparation, handling, monitoring and administration of antimicrobial drugs. The administration costs (needles, syringes, dressings, antiseptics, administration set, piggy bag) were NLG 5.80 per injection. The total administration costs per day, with 3 times daily administration are therefore NLG 17.40. The personnel costs for a tablet are about NLG 0.80 per dose (1 minute's work). The personnel costs

for a 15 min piggy bag infusion are about NLG 4 per dose. The total extra daily costs are therefore NLG 29.40 for 3 times daily iv administration of a cephalosporin and NLG 1.60 for twice daily oral administration. Considering the average use of about 6 dosage units iv cefuroxime in Dutch hospitals (22) the annual savings (purchase costs excluded) when 50% of parenteral cefuroxime would be replaced by an oral cephalosporin are: 27,80 per patient per day x 10 patients/day x 365 x 50% = NLG 50,735!
Purchase prices of oral cephalosporins are also considerably lower than those for parenteral second and third generation cephalosporins. In the Netherlands, Belgium and Germany, the daily difference in costs between iv cefuroxime 750 mg 3 times daily and oral cefuroxime axetil 500 mg twice daily is about NLG 35. If this difference is again multiplied by 3,650, the total annual savings would be NLG 63,875. The total annual savings, if 50% of parenteral cefuroxime could be replaced by oral cefuroxime, would therefore be about NLG 114,000. Considerable savings are therefore possible.
If the third generation cephalosporins are also replaced by oral cephalosporins, the savings are even greater: in Germany for instance, the average use of third generation cephalosporins in hospitals is about 5 DDD/100 bed days, which means that in a 500 bed hospital, about 25 patients are treated with parenteral third generation cephalosporins every day (23). The difference in daily purchase prices between cefotaxime (1 g 3 times daily) and the oral cephalosporins are about NLG 75. The difference in costs alone for these hospitals would be about NLG 342,000 per year per hospital, if 50% of parenteral third generation cephalosporins could be replaced by oral cephalosporins. None of the oral cephalosporins is active against *Pseudomonas aeruginosa*, however. Coupled with the savings described above, the cost implications of a successful sequential therapy are enormous.

METHODOLOGY OF A STUDY ON SEQUENTIAL THERAPY

Despite the arguments for a sequential therapy with cephalosporins, virtually no studies on this subject have been performed.

What should a good study on the feasibility of a sequential therapy look like?
Ideally, such a study should be randomized, double-blind and double-dummy.
If ethically acceptable, a third group should be included in which the treatment is stopped, when the other groups are either changed to oral therapy or maintained on iv administration. For most hospital infections the "generally accepted" duration of therapy is 7-10 days, so if a switch from iv to oral antibiotics takes place after 2-3 days, a third group is not necessary.
The type (and severity) of the infection to be treated should be clearly defined and the necessity for initial parenteral administration should be obvious. The criteria for clinical cure/improvement and failure should be clearly defined and all co-medication recorded.
The "drops-outs" should be carefully monitored to gain information on the practical feasibility of sequential therapy.
The switch from iv to oral cephalosporins should be clearly defined and be either based on clinical criteria (e.g. fever, leucocytes, oral administration possible) or a fixed day (day 2 or 3) after the initiation of therapy should be chosen. The exact duration of both oral and iv administration should be recorded. The criteria for stopping the treatment should also be prospectively defined.
The pathogen should be isolated and the MIC of the antibiotics to be studied determined and recorded to correlate the in-vitro activity, the route of administration, bacteriological cure rates and clinical efficacy.
The pharmacokinetics of both the iv and oral dosage form should be determined to be able to correlate the time above MIC with the clinical efficacy.
All side effects should be recorded, with special reference to infusion related side-effects and GI side-effects.

There is a need for studies to investigate the feasibility of sequential therapy with the newer oral cephalosporins, such as cefetamet, cefixime and cefpodoxime.

The results of the studies on sequential therapy with cephalosporins are summarised in Table 4. These studies were performed on patients with community-acquired lower respiratory tract infections, such as pneumonia, bronchitis and acute exacerbations of chronic bronchitis. These infections are usually not major indications for second and third generation cephalosporins and parenteral treatment is not indicated in all cases. The majority of these studies have not yet been published and were presented as abstracts of international congresses.

In three open, randomised comparative studies of cefuroxime and co-amoxiclav, both sequential therapies were equally effective (24-26). It is not clear whether initial parenteral treatment was necessary in all patients. The bacteriological eradication rates of pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis* by cefuroxime were high in all three studies. Virtually no *Enterobacteriaceae* were found in these patients.

The bacteriological cure rates for cefuroxime were better than those for parenteral cefotiam (27). All five infections caused by *Klebsiella pneumoniae* responded well to the treatment with cefuroxime. The total duration of treatment was longer in the cefuroxime group (12.6 days) than in the cefotiam group (8.3 days).

Cefpodoxime (200 mg twice daily orally) was compared with ceftriaxone (1 g once daily iv) in a group of patients with community acquired pneumonia and several other concurrent diseases such as cardiovascular disease, cancer, diabetes and respiratory insufficiency. It is not clear whether parenteral treatment with ceftriaxone was really indicated. The clinical and bacteriological results were similar in both groups. The commonest primary isolates were *Streptococcus pneumoniae* and *Haemophilus influenzae*. Parenteral second or third generation cephalosporins are not the drugs of choice for treatment of infections caused by these organisms. Gram-negative bacilli were found in 14% of the cases. The bacteriological cure rates with both cephalosporins were excellent (29).

TABLE 4

RESULTS OF SEQUENTIAL THERAPY WITH CEPHALOSPORINS

	Dosage (no. of daily doses)	Duration (days)	Clinical	Bacteriological cure (%)	References cure (%)
CEFU (n=246)	750 mg iv (3) 500 mg or (2)	2-3 5	95	82	24
AUG (n=245)	1 2 g iv (3) 625 mg or (3)	2-3 5	90	80	
CEFU (n=166)	750 mg iv (3) 500 mg or (2)	2-3 5	87	81	25
AUG (n=181)	1 2 g iv (3) 375 mg or (3)	2-3 5	93	89	
CEFU (n=137)	750 mg iv (3) 500 mg or (2)	2-3 5	86	94	26
AUG (n=134)	1.2 g iv (3) 625 mg or (3)	2-3 5	87	85	
CEFU (n=43)	1 5 g iv (3) 500 mg or (2)	3-4 8-10	96	82	27
CEFO (n=48)	2 g iv (2)	7-9	90	60	
CEFIX (n=44)	200 mg or (2)	11	94	89	28
CEFTR (n=47)	1 g iv (1)	11	96	84	
CEFPO (n=44)	200 mg or (2)	10	97	100	29
CEFTR (n=41)	1 g iv (1)	10	05	100	

AUG co-amoxiclav
CEFIX cefixime
CEFO cefotiam
CEFPO cefpodoxime
CEFTR ceftriaxone
CEFU cefuroxime

Cefixime (200 mg twice daily orally) was compared with ceftriaxone 1 g iv or im once daily for 11 days in the treatment of severe urinary tract infections. Both groups received initial treatment with ceftriaxone 2 g once daily iv for 4 days. The clinical and microbiological cure rates were similar for both groups. There were eight relapses or re-infections in each study group. Seven minor adverse events were seen in the ceftriaxone group, whereas no side-effects were observed with cefixime (28).

CONCLUSIONS

Although the results from these studies are encouraging, no definite conclusions on the feasibility of sequential therapy in clinical practice in hospital-acquired infections can be drawn. All studies examined patients with community-acquired respiratory tract infections and were not blinded; cefuroxime axetil may not be recommended for the treatment of hospital acquired infections, such as sepsis. Pharmacokinetic data at the time of change from iv to oral therapy were not given in any of the studies. Most infections described in the studies are usually treated with oral antibiotics from the start. The need for parenteral treatment was not clear.

In the treatment of serious infections, such as sepsis or hospital-acquired pneumonia, cephalosporins are often used in combination with aminoglycosides. By the time a pathogen is identified (after 2-3 days), many patients may be treated with an oral cephalosporin alone if the pathogen is susceptible.

The standardised switch after 2-3 days of iv treatment to oral antibiotics (clindamycin and metronidazole) in a Canadian hospital has resulted in saving of $20,000 per year. Reminders of iv to oral stepdown were sent to the nursing units with the parenteral dosage form, serving as a reminder to prescribers that oral therapy was an equally effective and a less expensive alternative to iv treatment. A similar stepdown programme has now started for ciprofloxacin and cefuroxime (30). The results of this study are awaited with interest.

Sequential therapy with iv and oral cephalosporins seems feasible in terms of pharmacodynamics. Serum concentrations of oral cefpodoxime, cefixime and cefetamet exceeding the MICs of these drugs for most *Enterobacteriaceae* persist for longer than for iv cefuroxime. The duration of activity of cefetamet is almost as long as that observed for iv cefotaxime. The newer oral cephalosporins, such as cefetamet, cefixime and cefpodoxime may offer advantages for sequential therapy compared with cefuroxime axetil. No oral cephalosporin is available with activity against *P. aeruginosa*.

Oral administration can lead to very significant savings in the purchase and administration costs of cephalosporins.

The clinical studies performed so far have all been performed wiln community-acquired respiratory tract infections, which are not major indications for (parenteral) cephalosporins.

Well-designed clinical studies, with good bacteriological and pharmacokinetic support are necessary to prove the feasibility of sequential therapy with cephalosporins in serious infections, such as hospital-acquired pneumonia, pneumonia caused by Gram-negative bacili, sepsis of unknown origin, urological sepsis, sepsis caused by Gram-negative bacilli and pyelonephritis.

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CHAPTER XII

CONCLUSIONS AND RECOMMENDATIONS

R. Janknegt

The majority of Dutch hospitals have created so-called antibiotic formularies with guidelines for the treatment of infectious diseases that are specific for that hospital or for a group of collaborating hospitals (regional formulary). A systematic study of these formularies was the main subject of this Thesis. Theoretically the basis of an antibiotic formulary is formed by concerns about therapeutic efficacy of antibiotics, emergence of resistance, toxicity and containment of costs.
The following statements summarize the findings in the preceding chapters and these can be used as a blue print for what I consider the optimal antibiotic formulary. These are summarized in Table 1.

TABLE 1

RECOMMENDATIONS FOR OPTIMAL ANTIBIOTIC POLICY

Guidelines based on local susceptibility data
Limited use of broad-spectrum agents
Involvement of the whole medical staff
Controlled compliance with the formulary
Frequent revisions of the formulary
Transparent selection criteria
Continuous effort to maintain high quality standard
Collection of data on antimicrobial drug use

- *All guidelines in the formulary are based on readily available data on antibiotic susceptibility of clinical isolates from the hospital, specified per ward and sample.*

It is highly desirable that the local susceptibility data form the basis of a local antibiotic policy. Susceptibility patterns may theoretically be quite different between hospitals. Susceptibility data from Dutch hospitals were not readily available, as was shown in Chapter 1. Only 5 out of 78 hospitals were able to provide these data in such a way that they could be used directly as a starting point for the preparation of an antibiotic formulary. This important criterion has not yet been fulfilled in the great majority of Dutch hospitals.

- The use of expensive and broad-spectrum antimicrobial agents is reduced by a strict antibiotic policy.

The use of antimicrobial agents is relatively low in hospitals in the Netherlands in comparison with hospitals in Germany or Belgium, as was shown in Chapter 3. The total use of antibiotics was 34 DDD per 100 bed days in Dutch hospitals, whereas the use of antibiotics in Germany and Belgium was 38 and 54 DDD per 100 bed days respectively. The use of broad-spectrum agents, such as third generation cephalosporins, aminoglycosides, antipseudomonal penicillins and fluoroquinolones was lower in the Netherlands than in both other countries. At least part of the differences between the use of antibiotics in the Netherlands and Belgium could be explained by differences in written antibiotic policy.
There are very few data on the quantitative and qualitative use of antibiotics in hospitals in other European countries.

- Authoritative medical staff members are involved in the preparation of an antibiotic formulary, which will increase the compliance with the antibiotic policy.

Once a formulary has been created a major concern is the compliance of the clinicians. The fact that a given hospital has a well-defined antibiotic policy, which is expressed in the antibiotic formulary, does not necessarily mean that this written policy is also kept to the letter in that hospital. This is shown in Chapter 2. We have introduced a ratio between the actual use of antibiotics and the number of indications from the antibiotic formulary. A very wide variation was observed between Dutch hospitals in this ratio, especially in the case of co-amoxiclav. These data underscore the need for a collaborative approach of medical staff, hospital pharmacist and microbiologist to reach consensus and thereafter maintain the compliance with the antibiotic policy in the hospital. Unless the antibiotic policy described in the antibiotic formulary is maintained in a strict manner, the enormous effort of preparing a local formulary can hardly be defended.

- The formulary must be revised at least every 3 years to keep up with all new developments in the treatment of infectious diseases and eventual changes in antibiotic susceptibility patterns.

A frequent update (every 2-3 years) of an antibiotic formulary is necessary to maintain a high level of compliance with the formulary and to include all new developments in antimicrobial drug therapy into the formulary. In most Dutch hospitals this is indeed the case. In a survey performed at the end of 1993, 56% of all formularies were less than three years old (Chapter 6). On the other hand 26% of these formularies was more than four years old. It seems unlikely that physicians comply with a formulary that is so old that is does not yet include the fluoroquinolones (which were introduced in 1988).

- The criteria on which a selection of antibiotics is made must be transparent and open for discussion within the medical staff.

Only two formularies from the Dutch hospitals have included a discussion section on the motivation of the antibiotic policy. One of these also contained data on the local susceptibility patterns (Chapter 1). This may be quite helpful in the preparation of a new antibiotic formulary. Most formularies contain no comments at all on the motivation of the choice of antibiotics.
In Chapter 10 the SOJA-score is proposed for making a rational choice within the group of fluoroquinolones. Although a certain degree of subjectivity is always present, the definition of "rational selection criteria" and their relative importance makes the choice of a certain antibiotic much more transparent and discussions on the importance of certain selection criteria become much more solid.

- A continuous effort (especially of the antibiotic formulary committee regarding literature study and discussions with clinicians) is needed to maintain a high quality of antibiotic policy.

This was investigated in Chapter 4 (bacterial bronchitis), Chapter 5 (pneumonia), Chapter 6 (sepsis), Chapter 7 (antimicrobial pro-

phylaxis in bowel surgery) and Chapter 8 (antimicrobial prophylaxis in gynaecological surgery).
The Dutch antibiotic formularies make a very restricted use of broad-spectrum antibiotics, such as the third generation cephalosporins, aminoglycosides and fluoroquinolones. This is also expressed by the drug utilisation data in Chapter 3.
A highly variable terminology was observed in the description of bacterial bronchitis. No less than 14 different terms were used to describe bacterial bronchitis. On the other hand very few differences were found in the treatment recommendations, amoxycillin and doxycycline being the most frequently used drugs. The lack of controlled clinical studies that have investigated the importance of dosing and duration of therapy in bacterial bronchitis is expressed in the Dutch formularies by the fact that guidelines for the duration of treatment are usually lacking.
A wide variety of antimicrobial agents was recommended by the Dutch antibiotic formularies in nosocomial pneumonia. Sixteen different drugs or drug-combinations were used by the Dutch formularies. Cefuroxime was the drug most often recommended.
For the treatment of sepsis of unknown aetiology aminoglycosides (in combination with a penicillin or cephalosporin) were the drugs of choice in almost all antibiotic formularies.
First and second generation cephalosporins and co-amoxiclav were the preferred agents in most formularies for antibiotic prophylaxis in surgery, but dose recommendations and the duration of prophylaxis were much more variable. A single dose was used in less than 50% of the formularies for bowel surgery and in 64% and 73% for vaginal and abdominal hysterectomy, respectively.
The newer third generation oral cephalosporins, such as cefixime, cefpodoxime proxetil and cefetamet offer the possibility of sequential oral therapy after an initial intravenous start. This may result in important savings in acquisition cost and other costs involved with intravenous therapy. Although this is an attractive idea, the clinical evidence of the feasibility of such sequential therapy is insufficient, as described in Chapter 11.
Most aminoglycosides are now used twice daily. The therapeutic range of aminoglycosides was based on the conventional 3 times daily dosing schedule. In Chapter 9 it is shown that the therapeutic

ranges of aminoglycosides have not been "updated" with the new situation. It must be kept in mind that such an update is not easy, as no clinical studies with twice daily aminoglycosides are available. The therapeutic range of amino-glycosides in patients receiving these drugs once daily or twice daily remains to be defined.

- The actual use of antibiotics and the antibiotic policy must be compared with that in other hospitals in the same country or abroad (European network) for optimal insight into the usefulness of antibiotic formularies.

A positive finding is that the use of antimicrobial agents in Dutch hospitals is low in comparison with that in Germany and Belgium and wide-spectrum antimicrobial agents are used to a limited degree. As such, this Dutch experience could perhaps be followed by other countries. An "European network" of hospitals that are able to provide data on antibiotic use, susceptibility data and antibiotic policy is desirable to improve the communication between European countries.

It is concluded that the availability of local susceptibility data leaves much to be desired. Without these data it is impossible to defend the wide differences in antibiotic policy observed in the Dutch antimicrobial formularies.
The motivation of the choice for a given antibiotic in a specific infection is quite helpful in the discussions with the medical staff and will improve compliance with the antibiotic policy. The SOJA system may be a useful tool in transparent drug-decision making.

SUMMARY

A rational use of antibiotics (drugs used for the treatment of bacterial infectious diseases) is indicated to reduce the development and spread of resistant bacteria as well as from an economic point of view. The cost of antibiotics contributes for 10-20% to the total drug cost in hospitals. Most Dutch hospitals have created so-called "antibiotic formularies" with guidelines for the treatment of infectious diseases. These guidelines are specific for a hospital or for a group of collaborating hospitals in the same region (regional formularies).
In this thesis, the Dutch antibiotic formularies have been studied.

The rationale of this study is described in **Chapter 1** and a short summary of the various investigations is given. This Chapter also presents an overview of Dutch antibiotic formularies. A total of 38 formularies were received, used in 78 hospitals. Of these formularies 43% were less than 3 years old. Despite the fact that there is a consensus on the importance of local susceptibility patterns as the basis for antibiotic policy, these data were readily available from only a limited number of hospitals.

The correlation between the written antibiotic policy, as expressed in the antibiotic formularies, and the actual use of antibiotics in 20 Dutch hospitals is studied in **Chapter 2**. The number of DDD per 100 bed days was divided by the number of indications for a given antibiotic in the antibiotic formulary. This ratio was highly variable for most groups of antibiotics. These differences could partly be explained by the use of antibiotics in antibiotic prophylaxis in surgery and by differences in the size and status of the hospital. Discrepancies between the written and actual antibiotic policy may also play a role.

A study on the use of antibiotics in hospitals in the Netherlands, Germany and Belgium is presented in **Chapter 3**. The use of these drugs was expressed as Defined Daily Doses (DDD, an international standardised daily dose for each antibiotic) per 100 bed days. The total use of antibiotics was significantly higher in

Belgium (55.6 DDD/100 bed days in the Dutch speaking part of Belgium and 52.0 DDD/100 bed days in the French speaking part) in com-parison with Germany (37.9 DDD/ 100 bed days) and the Netherlands (34.1 DDD/100 bed days). The use of co-amoxiclav, first and second generation cephalosporins, aminoglycosides and fluoroquinolones was much higher in Belgium than in both other countries. A part of this difference could be explained by differences in written antibiotic policy in Belgium compared to the Netherlands.

The antibiotic policy in Dutch hospitals in bacterial bronchitis, pneumonia and sepsis is described in **Chapters 4**, **5** and **6**, respectively.
The nomenclature of bacterial bronchitis in the formularies was highly variable and a clinical description was lacking in most formularies. Amoxycillin, doxycycline and co-trimoxazole were the most frequently used antibiotics in this infection. All formularies recommended oral administration of these drugs. The large majority of formularies advised an amoxycillin dose of 750 mg 3 times daily.
The recommendations for pneumonia with unknown pathogen were highly variable. In the treatment of community-acquired pneumonia no less than 13 different (combinations of) intravenous antibiotics were recommended by the formularies. Amoxycillin was preferred in 45% of them. Sixteen different (combinations of) antibiotics were recommended for hospital-acquired pneumonia. The guidelines for dosage were also highly variable. The daily dose of benzylpenicillin ranged between 1 and 12 million units.
A similar pattern was observed in sepsis. In sepsis with unknown pathogen, a total of 16 different intravenous antibiotics (combinations) were used. Aminoglycoside-containing regimens were recommended by the large majority of formularies. These drugs were most frequently combined with amoxycillin, co-amoxiclav and cefuroxime.

In a number of surgical procedures, it is necessary to administer prophylactic antibiotics to prevent surgical wound infections. This

is especially important in contaminated surgery, such as bowel surgery, as well as those surgical procedures in which the consequences of a wound infection are very serious, such as in prosthetic hip surgery. The Dutch policy regarding the use of antibiotics in surgical prophylaxis is presented in **Chapters 7** and **8**. Co-amoxiclav and first or second generation cephalosporins (with or without metronidazole) were the most frequently used antibiotics in bowel surgery. Multiple-dose regimens were used in most formularies ranging from 52 to 66% for various forms of bowel surgery.
Co-amoxiclav was the most frequently used drug in gynaecological and obstetric surgery. A single dose prophylaxis was recommended by 64% of the formularies for vaginal hysterectomy, by 73% for abdominal hysterectomy and by 50% for caesarian section.

Chapter 9 discusses the use of aminoglycosides in Dutch hospitals. This group of antimicrobial agents has a narrow therapeutic margin, i.e. serious nephrotoxic and ototoxic reactions may occur. The serum concentration of aminoglycosides is routinely assayed to prevent toxic reactions as much as possible. Aminoglycosides were always given in a 3 times daily manner. From recent studies it has become evident that a once daily dosage is as effective and probably less nephrotoxic.
We showed that 72% of 65 Dutch hospitals used aminoglycosides in a twice daily manner, whereas 18% used a once daily method and only 10% still used the conventional 3 times daily method. The twice daily dosing method turned out to be a compromise between once daily (microbiologist and hospital pharmacist) and 3 times daily (clinicians). Only a limited number of hospitals have adjusted the "normal values" for peak and trough concentrations of aminoglycosides to the different dosage regimens. The serum concentrations of aminoglycosides in patients receiving these drugs in a once daily or twice daily manner are difficult to interpret, due to the lack of studies investigating the relationships between serum concentrations and efficacy or toxicity.

For a good compliance of the members of the medical staff it is essential that it is clear to all users of the formulary why certain decisions have been made. In the selection of a drug from a specific pharmaceutical group, a wide variety of (rational and emotional) selection criteria may play a role. **Chapter 10** proposes the SOJA (System of Objective Judgement Analysis) system to make drug-decisions in a transparent way. Selection criteria are defined and each of these has a certain weighting factor. By means of this method a drug-selection has been made for the fluoroquinolones. Ofloxacin shows a higher score than ciprofloxacin and pefloxacin.

Chapter 11 discusses various aspects of a sequential therapy with intravenous and oral cephalosporins. Oral administration may offer advantages concerning lower acquisition cost, reduction in work load on the hospital ward, better patient-comfort and the lack of infusion-related complications. Reliable absorption is essential for a good antimicrobial activity. A change from iv to oral cephalosporins after 3-5 days may result in substantial savings, because of the lower acquisition cost and the lower cost for administration of oral drugs in comparison with intravenous antibiotics. No conclusive clinical evidence is available, however to demonstrate that such an approach to infectious diseases is achievable. Recommendations are given for future research in this field.

Chapter 12 summarizes the most important conclusions of the preceding chapters. Recommendations for an "ideal" antibiotic policy are given.

SAMENVATTING

Een rationeel gebruik van antibiotica (middelen die worden toegepast bij de behandeling van bacteriële infectieziekten) is zowel van belang om de ontwikkeling en verspreiding van resistente bacteriën te voorkomen alsmede vanwege de hoge kosten die verbonden zijn aan de toepassing van antibiotica. De kosten van antibiotica bedragen 10-20% van de totale geneesmiddelkosten in ziekenhuizen.

De meeste Nederlandse ziekenhuizen hebben zogenaamde "antibiotica formularia" in gebruik met richtlijnen voor de behandeling van infectieziekten. Deze richtlijnen zijn specifiek voor dit ziekenhuis of voor een groep van nabijgelegen ziekenhuizen (regionale formularia).

In dit proefschrift worden de Nederlandse antibiotica formularia bestudeerd.

In **Hoofdstuk 1** wordt beschreven waarom dit onderzoek werd uitgevoerd en wordt een korte samenvatting gegeven van de verrichte onderzoeken. Tevens wordt een overzicht gegeven van de in ons land gebruikte antibiotica formularia. Er werden in totaal 38 formularia ontvangen, die in 78 Nederlandse ziekenhuizen werden toegepast. Van deze formularia was 43% minder dan 3 jaar oud. Ondanks het feit dat iedereen het erover eens is dat de richtlijnen voor de behandeling van infectieziekten zouden moeten worden afgestemd op de beschikbare gegevens van het lokale of regionale microbiologisch laboratorium ten aanzien van de gevoeligheid van bacteriën voor diverse antibiotica, bleken deze gegevens slechts in beperkte mate beschikbaar te zijn.

In **Hoofdstuk 2** worden de gegevens ten aanzien van het geschreven antibiotica beleid, zoals dat uitgedrukt is in de antibiotica formularia en het daadwerkelijke gebruik van antibiotica in 20 Nederlandse ziekenhuizen aan elkaar gecorreleerd. Hiertoe werd het aantal DDD's per 100 bed dagen gedeeld door het aantal indicaties voor het betreffende middel in het antibiotica formularium. De ratio hiertussen bleek zeer variabel voor de meeste groepen van antibiotica. Deze verschillen konden deels worden

verklaard door het profylactische gebruik van antibiotica en door verschillen in de functies van de ziekenhuizen (basis ziekenhuis of academisch ziekenhuis). Ook verschillen tussen het geschreven beleid (formularia) en het daadwerkelijk gevoerde beleid kunnen hiertoe hebben bijgedragen.

In **Hoofdstuk 3** wordt een onderzoek gepresenteerd naar het gebruik van antibiotica in ziekenhuizen in Nederland, Duitsland en België. Het gebruik werd uitgedrukt in Defined Daily Doses (DDD, een internationale gestandaardiseerde dagdosis van ieder antibioticum) per 100 bed dagen. Het totale gebruik van antibiotica was significant hoger in België (55,6 DDD per 100 bed dagen in Vlaanderen en 52,0 in Wallonie) dan in Duitsland (37,9 DDD/100 bed dagen) en Nederland (34,1 DDD/ 100 bed dagen). Vooral het gebruik van amoxicilline-clavulaanzuur, eerste en tweede generatie cefalosporines, aminoglycosiden en gefluorideerde chinolonen was veel hoger in België dan in de beide andere landen. Een deel van dit verschil kon worden verklaard door een ander (geschreven) antibioticabeleid in Belgie in vergelijking met Nederland.

In de **Hoofdstukken 4, 5** en **6** wordt het beleid in de Nederlandse ziekenhuizen beschreven bij bacteriële bronchitis, pneumonie en sepsis. De gebruikte terminologie van het ziektebeeld bacteriële bronchitis in de formularia is zeer divers en een duidelijke klinische omschrijving ontbreekt zelfs in de meeste formularia. Amoxicilline, doxycycline en cotrimoxazol zijn de meest gebruikte antibiotica bij deze infectie. Alle formularia adviseren een orale toediening. De grote meerderheid van de formularia adviseert een dosering van 3 x daags 750 mg amoxicilline.
Bij pneumonie met een onbekende verwekker blijkt er een grote variatie te bestaan in de aanbevelingen in de formularia. Bij de behandeling van pneumonie met onbekende verwekker, verkregen buiten het ziekenhuis, werden liefst 13 verschillende intraveneuze antibiotica of combinaties van antibiotica toegepast. In 45% van de formularia werd amoxicilline aanbevolen. Bij pneumonie verkregen in het ziekenhuis werden zelfs 16 verschillende antibiotica (combinaties) toegepast. Ook de richtlijnen voor de dosering liepen sterk uiteen: de dosering voor benzylpenicilline lag

tussen 1 en 12 miljoen IE per dag.
Bij het zeer ernstige ziektebeeld sepsis werd opnieuw een groot aantal verschillende intraveneuze antibiotica toegepast. Bij sepsis met onbekende verwekker werd in vrijwel alle formularia een aminoglycoside aanbevolen, in combinatie met amoxicilline, amoxicilline-clavulaanzuur of cefuroxim. In totaal werden 16 verschillende antibiotica (combinaties) toegepast.

Bij een groot aantal chirurgische ingrepen is het noodzakelijk gebleken om profylactisch antibiotica toe te dienen teneinde wondinfecties te voorkomen. Dit is vooral van belang indien de ingreep plaatsvindt in een "gecontamineerd" gebied zoals de darm, of indien de gevolgen van een eventuele wondinfectie zeer ernstig kunnen zijn, zoals bijvoorbeeld bij een "totale heup". In de **Hoofdstukken 7 en 8** wordt een overzicht gegeven van het beleid in Nederlandse ziekenhuizen ten aanzien van de antibiotische profylaxe in de chirurgie. In de darmchirurgie worden vooral amoxicilline-clavulaanzuur en eerste of tweede generatie cefalosporines, al dan niet in combinatie met metronidazol toegepast. In de meeste formularia (52 tot 66%) werden meer-doses profylaxe-regimes toegepast. In de gynaecologische en obstetrische chirurgie was amoxicilline-clavulaanzuur veruit het meest toegepaste middel. Een 1-dosis profylaxe werd aanbevolen door 64% van de formularia voor vaginale hysterectomie, door 73% voor abdominale hysterectomie en door 50% voor een keizersnede.

In **Hoofdstuk 9** wordt het gebruik van de aminoglycosiden in Nederlandse ziekenhuizen bestudeerd. Deze groep van antibiotica heeft slechts een beperkte "therapeutische breedte", dat wil zeggen dat ernstige toxische reacties, met name op de nierfunctie en het gehoor, kunnen optreden. Daarom wordt van deze middelen de concentratie in het bloed bepaald om deze toxische reacties zoveel mogelijk te kunnen voorkomen. Traditioneel werden deze middelen altijd 3 x daags toegepast. Uit recent onderzoek is gebleken dat een 1 x daagse toepassing even effectief is en mogelijk minder toxisch is voor de nier. Uit het in dit hoofdstuk beschreven onderzoek blijkt dat 72% van de 65 ondervraagde Nederlandse ziekenhuizen een 2 x daagse dosering gebruiken, 18% 1 x daags en 10% 3 x daags. Dit ondanks het feit dat er vrijwel geen literatuur over een 2 x daagse toepassing beschikbaar is. De 2 x daagse toepassing bleek een compromis te zijn tussen 1 x daags (microbioloog en apotheker) en 3 x daags (clinici). Niet alle ziekenhuizen hadden de "normaalwaarden" voor de "top en dal" aminoglycoside-concentraties in serum aangepast aan het veranderde doserings-regime. De serumconcentraties van aminoglycosiden bij een 1- of 2 x daagse toepassing zijn moeilijk te correleren aan effectiviteit en toxiciteit, door het ontbreken van onderzoek.

Voor een goede "gedragenheid" onder de medische staf van een formularium is het van groot belang om duidelijk te maken waarom een bepaalde beleidsbeslissing is genomen. Bij de keuze van een geneesmiddel binnen een bepaalde farmacotherapeutische groep spelen een groot aantal rationele en emotionele factoren een rol. In **Hoofdstuk 10** wordt een scoringssysteem opgevoerd (SOJA score), waarbij keuzecriteria worden gedefinieerd en elk criterium een relatief gewicht krijgt. Door middel van deze methode wordt dan een preparaatkeuze gemaakt voor de gefluorideerde chinolonen. Ofloxacine vertoont een hogere score dan de beide andere middelen ciprofloxacine en pefloxacine.

In **Hoofdstuk 11** worden de diverse aspecten van een oraal vervolg van een parenteraal gestarte therapie met cefalosporines besproken. Orale behandeling biedt voordelen ten aanzien van kosten, werkdruk, patiënten-comfort en het minder optreden van infuus-gerelateerde bijwerkingen. Voor een goede werking is echter een betrouwbare orale absorptie noodzakelijk. Het blijkt dat een snelle overgang naar een orale behandeling van infecties tot zeer aanzienlijke kostenbesparingen kan leiden, door een vermindering van de personeelskosten en de veel lagere aanschafprijs van orale middelen in vergelijking met parenterale middelen. Er is echter nog vrijwel geen onderzoek verricht dat "hard" maakt dat een dergelijke aanpak van ernstige infectieziekten in het ziekenhuis daadwerkelijk mogelijk is. In dit hoofdstuk worden aanbevelingen gedaan hoe een dergelijk onderzoek eruit zou kunnen zien.

In **Hoofdstuk 12** worden de belangrijkste conclusies van de voorgaande hoofdstukken samengevat en worden aanbevelingen voor een "ideaal" antibioticumbeleid gedaan.

DANKWOORD

Aan dit proefschrift heeft een groot aantal mensen in aktieve of passieve zin een bijdrage geleverd.
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Drs. H. Brummelman, arts, verbonden aan Roussel Nederland BV en de heer R. Kruijff, verbonden aan Hoechst Holland Pharma

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Mevr. B. Monsma-Wielens en mevr. M. Bos-Mertens, secretaresses van de afdeling Klinische Farmacie van het Maasland Ziekenhuis te Sittard. Vooral in de maanden januari tot april kwam ik op de meest ongelegen momenten binnenvallen om "snel" even iets te printen. Dat "iets" was dan meestal een vrij tot zeer omvangrijk document. Dat zal nu zeker minder worden, doch helaas waarschijnlijk niet al te veel.
Alle apothekers-assistentes van het Maasland Ziekenhuis. Jullie hebben mij de gelegenheid gegeven om me af en toe op mijn kamer terug te trekken om te werken aan dit proefschrift. Met name in Geleen was de concurrentieslag voor een plekje achter de PC soms hevig. Dank voor jullie medewerking.
En dan tenslotte, zoals gebruikelijk "Last but not least", dank ik het thuisfront. Lieve Irene, Ronald en Laura. Jullie hebben mij de gelegenheid gegeven om thuis hard te werken aan de promotie. Hoewel de overgrote meerderheid van het werk zich in de huiskamer afspeelde, waardoor ik in ieder geval tot op zekere hoogte bij het sociale gebeuren betrokken bleef, waren er ook talrijke momenten dat ik mij achter de PC moest terugtrekken. Jullie hebben daar bewonderenswaardig weinig over geklaagd.

CURRICULUM VITAE

Robert Janknegt werd geboren op 24 juli 1953 te Koog aan de Zaan. Hij behaalde in 1971 het diploma HBS-B aan de Rijksscholengemeenschap Noord Kennemerland te Alkmaar. Van 1972 tot 1980 studeerde hij farmacie aan de Universiteit van Amsterdam. Hij startte vervolgens de opleiding tot ziekenhuisapotheker in het Maasland Ziekenhuis te Sittard (opleider Prof. dr. F.W.H.M. Merkus) en hij werd op 1 januari 1983 geregistreerd.
Hij was van januari 1983 tot september 1987 werkzaam in het Medisch Centrum Alkmaar, waarna hij weer terugkeerde naar Sittard. Thans is hij als ziekenhuisapotheker verbonden aan de Stichting Ziekenzorg Westelijke Mijnstreek en is tevens toezichthoudend apotheker van de zwakzinnigeninrichting Pepijnklinieken te Echt. Sinds begin 1992 is hij daarnaast als adviserend apotheker verbonden aan de zorgverzekeraar LIASS.

STELLINGEN

Behorend bij het proefschrift

ANTIBIOTIC POLICY IN DUTCH HOSPITALS

A survey of Dutch antibiotic formularies

R. Janknegt

Nijmegen, 12 oktober 1994

1. De beschikbaarheid van gegevens over de in-vitro gevoeligheid van micro-organismen voor antimicrobiële middelen in Nederlandse ziekenhuizen laat nog veel te wensen over.
(dit proefschrift)

2. Het verbruik van antibiotica in Nederlandse ziekenhuizen is laag in vergelijking met ziekenhuizen in Duitsland en België.
(dit proefschrift)

3. Voor een breed draagvlak is het van groot belang dat de medische staf op ruime schaal betrokken is bij het opstellen van een antibioticum formularium.
(dit proefschrift)

4. Het gebruik van antibiotica komt niet altijd goed overeen met de richtlijnen in het formularium.
(dit proefschrift)

5. Het opstellen van een antibioticum formularium in ieder ziekenhuis afzonderlijk is alleen te verdedigen als dit gebaseerd is op lokale gevoeligheidsgegevens en indien dit formularium een breed draagvlak heeft in het betreffende ziekenhuis. (dit proefschrift)

6. Bij de behandeling van sepsis met onbekende verwekker wordt een zeer groot aantal verschillende antibiotica toegepast in Nederlandse ziekenhuizen.
(dit proefschrift)

7. Een sequentiële therapie met intraveneuze en orale cefalosporines is vanuit financieel oogpunt zeer aantrekkelijk, doch is klinisch onvoldoende gedocumenteerd.
(dit proefschrift)

8. Het toepassen van een transparant beslissingsmodel bij de keuze van een geneesmiddel uit een farmacotherapeutische groep biedt grote voordelen boven vage "wetenschappelijke afwegingen".
(dit proefschrift)

9. De Taxeprijs van generieke geneesmiddelen dient te worden aangepast aan de gangbare marktprijs.

10. Zolang de K.N.M.P. in haar stellingname tegen "postorderfarmacie" niet openlijk het criterium "het kost ons geld" noemt, is het standpunt van de K.N.M.P. weinig geloofwaardig.

11. Het verdient sterke aanbeveling om de details van de maatregelen die door het ministerie van WVC worden genomen in het vervolg langer dan 5 minuten van te voren bekend te maken aan verzekeraars, voorschrijvers en afleveraars.

12. Goede onderlinge verhoudingen in vriendschap en waardering vormen de beste basis voor wetenschappelijk onderzoek.

13. Een rookverbod in (gedeelten van) restaurants dient verplicht te worden, opdat ook astma patiënten uit eten kunnen gaan zonder tweemaal een rekening gepresenteerd te krijgen.